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THE PRINCIPLES OF CLINICAL PATHOLOGY IN PRACTICE

GEOFFREY BOURNE & KENNETH STONE

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THE PRINCIPLES OF CLINICAL PATHOLOGY IN PRACTICE

A GUIDE TO THE INTERPRETATION OF LABORATORY INVESTIGATIONS FOR THE USE OF THOSE ENGAGED IN THE PRACTICE OF MEDICINE

BY

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PREFACE

THE interpretation of clinical pathological findings in disease by the practitioner of medicine is a subject of great importance and of some difficulty.

It is important because without knowledge of the degree to which the various laboratory tests are applicable in any given case the clinician is too much in the hands of his laboratory colleague; the present undue ascendancy of the latter in the field of clinical medicine being probably directly ascribable to this.

It is difficult because it is now impossible that any practitioner shall have had a training in more than one or two such special subjects, so as to be able to assess for himself the probable value of an investigation.

The present work is an attempt to collect what are accepted as the most constant clinical pathological findings in disease, to state when the result of a test whether positive or negative is of value, and to record when such a test is worth doing and when it is incapable of giving help.

Text-books of clinical pathology are for the most part concerned with the subject from an academic point of view and become filled with minutiae of technique. Text-books of medicine cannot afford to emphasize the interpretation of clinical pathological findings without losing balance or becoming unduly bulky. It is hoped that both faults have been avoided herein. No medical man should ask for a special investigation without knowing to what extent a positive, a negative, or an equivocal answer will react upon his clinical conception of the case. The contents of this book have been chosen to assist him in using this knowledge.

Facts likely to be of assistance to the clinician have been included, facts unlikely to be of use have been excluded. Laboratory methods cannot depose clinical methods from their importance in the examination of the patient: their use must rather be complementary to them.

An appendix has been added describing the precautions

to be taken in the transference of specimens by post or otherwise to the pathological laboratory.

The subject-matter of most of the chapters has been arranged in a uniform manner. Under the heading 'General Considerations' has been gathered sufficient of the facts concerning the pathology of the disease to enable the origin of the clinical pathological findings to be understood. The chief of these are then enumerated. Finally, the bearing of each individual finding upon diagnosis, prognosis, and treatment is discussed.

It should be remembered that the contents of this book have reference only to results obtained by competent and careful work. No patient's life or health should be allowed to depend upon results obtained by semi-skilled laboratory assistants. No report at all is often less misleading than is one so obtained.

The writers wish to express their indebtedness to Drs. G. Linder, P. H. Martin, and J. Maxwell, who have kindly given valuable advice with regard to the sections dealing with diabetes and nephritis, tropical diseases, and diseases of the liver, respectively, and to Mrs. Geoffrey Bourne for much invaluable help in reading and correcting the proofs.

A list of some of the books to which reference has been made is given on the next page.

G. B.
K. S.

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December, 1928.

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Vincent's Angina.
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VI. FOCAL INFECTIONS AND DISEASES ARISING THEREFROM

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- Pyorrhoea Alveolaris.
- Tonsillitis.
- Sinusitis.
- Chronic Cholecystitis.
- Prostatitis and Vesiculitis.
- Endometritis and Salpingitis.

Diseases resulting from Focal Sepsis :

- Arthritis.
- Peptic Ulcer.
- Anaemia.
- Mental Disorders.
- Iritis.

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CHAPTER I

BLOOD INFECTIONS

SEPTICAEMIA

General Considerations

Septicaemia, strictly speaking, is any condition in which organisms can be recognized as being present in the blood-stream. The number of diseases in which such recognition is possible has rapidly increased with advances in bacteriological technique. The following organisms have been obtained from the blood: streptococci, staphylococci, pneumococci, *B. influenzae*, *meningococcus*, *gonococcus*, *B. typhosus* and *B. paratyphosus*, the *B. dysenteriae*, *B. pestis*, *B. anthracis*, *Micrococcus melitensis*, *B. coli*, and *B. welchii*. Many diseases not classed as septicaemias by the clinician are accompanied by a definite blood infection. Among these are pneumonia, typhoid fever, and cerebro-spinal fever. It seems probable that the list of diseases accompanied by a recognizable haemic infection is likely eventually to become considerably longer.

The term septicaemia is reserved, however, in clinical medicine for febrile illnesses accompanied by the presence in the blood of an organism, generally one of the common pyogenic cocci. Other clinical characteristics are purpura, haematuria, articular lesions, and rigors. The organisms most commonly involved are streptococci, pneumococci, staphylococci, and gonococci. In such cases the blood infection is generally to be traced originally to some local focus of infection. Streptococcal septicaemia is frequently secondary to erysipelas, tonsillitis, otitis media, and puerperal sepsis; pneumococcal septicaemia often follows directly upon a pneumonia or an otitis media; staphylococcal septicaemia is commonly a sequel of furunculosis and osteomyelitis.

In health many potentially pathogenic organisms live on the skin and in the intestinal canal; some of these probably actually get as far as the blood-stream in very small num-

bers, where they are destroyed or rendered inactive, and whence they are rapidly excreted by the kidneys.

There would seem to be two factors necessary for the production of a septicaemia:

1. Continued doses or great virulence of a pathogenic organism.
2. Lowered resistance on the part of the patient.

Diabetes and chronic nephritis are good examples of the second of these two causes, but it is to the first that attention should principally be directed.

The first logical step in the treatment of any septicaemia must be an attempt to discover and to eradicate the focus whence infection is originating. Examples of this are to be found in cases of septicaemia following acute otitis media complicated by phlebitis of the internal jugular vein, and in cases of puerperal septicaemia. Ligature of the internal jugular vein in the one case, and removal of infected material from the uterus in the other, is usually followed by a rapid disappearance of the organism from the blood. It is logical to conclude that many cases of septicaemia are due to continued infection originating in some focus less obvious than the examples here mentioned. In one such case the focus was found, at the autopsy, to be a small retro-pharyngeal abscess, and it is possible that had this been discovered during life its successful treatment might have led to a different issue.

Briefly, therefore, the pathological steps in the development of a septicaemia are:

1. The organism penetrates the normal defensive system of the body.
2. The organism reaches a position in the tissues where it proliferates.
3. Blood invasion takes place and continues.
4. Proliferation occurs independently in the blood-stream.

Each of these processes has a therapeutic counterpart:

1. Raising the general health of the patient.
2. Drainage or removal of the deep-seated focus.

3 and 4. Intravenous serum treatment.
Sensitized vaccines.
Intravenous disinfectants.
Transfusion.

Pathological Findings in Septicaemia

The main pathological abnormalities in septicaemia are:

I. Bacteriaemia.
II. Bacteriuria.
III. Leucocytosis.
IV. Severe secondary anaemia.

Bacteriaemia

Though organisms are rarely present in the blood in such quantities as to be manifest in a stained blood film, yet in fulminating cases this may occur. The organisms most frequently met with in such circumstances are the *Meningococcus* and *Bacillus anthracis*.

Blood-culture, however, is the method by which the presence of bacteriaemia is most constantly determined. The success or failure of the procedure depends upon a number of factors. The organisms may be present in such small numbers that they may be caught up mechanically and hidden in the blood clot. The organisms may be of such feeble growth that antibodies are present in sufficient concentration in the blood withdrawn to inhibit their growth. The organisms may only grow anaerobically. Thus if a specimen of blood of about 10 c.cm. be placed in a single broth tube and incubated, a negative result, even in the presence of a slight bacteriaemia, may very well follow. It is wise, therefore, to dilute the blood with a considerable quantity of the nutritive medium, to cultivate some of it anaerobically, and to give growth a sufficient length of time, even up to ten days, in which to appear.

Libman's method of dilution is to place the blood, 5–10 c.cm. in amount, in a flask containing from 100 to 150 c.cm. of broth. Another method is to place a few drops in a number of separate broth tubes. In this way one or two of the tubes can be cultivated anaerobically and the

rest in the usual manner. In suspicious cases blood-cultures should be repeated several times.

A positive blood-culture is diagnostic of septicaemia. Septicaemia may be present though blood-cultures remain negative, but repeatedly negative results make the diagnosis progressively less likely.

Growth of the same organism in all tubes means a positive result. The presence of *Staphylococcus albus* generally indicates contamination from the skin, but its power to ferment mannite should be investigated. Pathogenic staphylococci ferment mannite, non-pathogenic ones do not.

Bacteriuria

One of the normal functions of the kidney is the excretion of any stray organisms that may from time to time reach the blood-stream. Such an entry into the blood probably occurs in small numbers in healthy people. Septicaemia, however, does not follow, for the patient's resistance is high, and there is no focus of infection. When streptococci are injected experimentally into the circulation of rabbits the very great majority of organisms are excreted by the kidneys within a few hours.

Thus a continued blood infection is almost bound to have as its corollary a continued excretion of the infecting organisms by the kidney. In cases of suspected septicaemia, therefore, where blood-culture has proved repeatedly negative, it is sometimes worth while cultivating a catheter specimen of the urine. When the urine is being sent to a laboratory in a bottle boiled upon the premises, a rubber or glass stopper should be used, as a cork, even after boiling, remains a fertile source of contamination.

The commonest contaminations of urine specimens are the *Bacillus coli*, the *Streptococcus faecalis*, and the *Staphylococcus epidermidis albus*. The first and last rarely cause septicaemia. The last will not ferment mannite. The *Streptococcus faecalis* is, however, quite a common blood invader in cases of malignant endocarditis, and its presence in the urine of a presumably septicaemic patient is not necessarily due to contamination. Certain organisms so obtained may

be tested against the patient's serum for the presence in the latter of agglutinins or complement-fixing antibodies. This test, in skilled hands, is particularly valuable in cases of septic endocarditis. Urine is easily contaminated; thus a positive result should be confirmed by examination of a second specimen.

Leucocytosis

Except in fulminating cases lasting only for a few days leucocytosis is a constant finding in septicaemia. In the majority of cases the white count is between 15,000 and 30,000, but higher figures are not uncommon. The increase is in the polymorphonuclear leucocytes. Coincident with this there is a diminution in the number of eosinophiles. A few myelocytes may be present.

The degree of leucocytosis is to a rough extent proportional to the severity of the infection, but this is far from being a fixed rule.

It may be stated with a fair degree of accuracy that, in the case of septicaemia where the patient is acutely ill, and there is no leucocytosis, or perhaps a leucopenia, death is imminent; that where a patient with fever has remained severely ill for more than a week, and there is no increase in the white count above normal, the case is one, not of septicaemia, but of some other condition, such as acute tuberculosis or typhoid fever; that in a case of septicaemia where the original high white count is falling and there is no corresponding improvement in the clinical condition the prognosis becomes grave.

Simon (1) lays great stress upon the differential count in the diagnosis and prognosis of septicaemia and other septic conditions. He states that in most cases of leucocytosis the polymorphonuclear cells are generally increased in proportion to the total number, 'usually ranging between 80 and 90 per cent. Higher percentages indicate an especially severe infection. Coincident with the neutrophilic increase there is a decrease or absence of eosinophiles.' He further states, 'If in a clinically manifest case of septicaemia the eosinophiles are found in normal or

increased numbers, it may be taken for granted either that the patient is improving or that some other factor is simultaneously active, which in itself would lead to eosinophilia'.

Anaemia

In many types of septicaemia, particularly those caused by streptococci and staphylococci, there is a more or less rapid destruction of red blood-cells. The red blood count may easily fall to below 3,000,000. Puerperal septicaemia provides perhaps the most extreme type. In this condition the blood destruction is particularly rapid. Where the fall in the count is more gradual the haemoglobin percentage is lower in proportion, giving a colour index of well below one, and a count having the characteristics of a chlorotic anaemia. This, in addition to the leucopenia, is a distinguishing point between septicaemia and pernicious anaemia, in which fever is not uncommon.

Treatment

The chief therapeutic aims are:

1. To remove a focus whence organisms are disseminated into the blood-stream.
2. To increase the patient's immunity passively by appropriate sera or actively by vaccines, preferably sensitized.
3. To treat the anaemia by transfusion.

The first of these is a purely clinical problem. Sera should be given as early as possible in massive doses, if their best effect is desired. Repeated daily injections of 10 c.cm. are sometimes useless, where two successive doses of 100 c.cm. may have an effect.

Sensitized vaccines may be given safely in severe infections, as no negative phase results. Doses may be large and should be given upon successive days. Unsensitized vaccines may be of use in chronic septicaemias. Doses should be small and repeated at intervals of not less than six days.

Transfusion in septicaemia serves a double purpose.

Anaemia is to some extent treated, and healthy leucocytes and antibodies are added. In chronic cases previous treatment of the donor by vaccines can be resorted to in order to prepare a blood rich in antibodies against the organism infecting the patient. The great importance of obtaining a positive blood-culture, from the point of view of specific treatment, is thus made manifest.

The method first introduced by Almroth Wright and his co-workers (2) and named by them immuno-transfusion appears to hold promise in cases of severe infection. He recognizes two varieties of immunity: firstly, that which is present in the blood of all people to a greater or less degree and which requires, therefore, no mobilization before being put into action; secondly, that which the presence of an invading organism excites. The former he names aphylactic immunity and the second the epiphylactic response.

It is the second which is peculiarly lacking in severe persistent infections. The phagocytes have been so continuously and unavailingly stimulated that they have, so to speak, become weary and unable to respond further. It is clear that the blood of healthy donors will contain only the protection present in normal healthy adults, and it is with the idea of exciting in these, in addition, the epiphylactic reaction that immuno-transfusion has been devised, such immunized healthy adults being then used as donors. It has been found that the epiphylactic response is not specific, and that it can be excited by an injection, five hours before, of staphylococcal vaccine (1,000 millions) or *B. typhosus* vaccine (250 millions).

The procedure is as follows:

1. The patient is believed to be suffering from a severe infection against which he is not reacting.
2. It is believed that a temporary artificial increase in his immune bodies will allow his own reactive powers time in which to recover.
3. A healthy donor, of the right blood-group and free from syphilitic and malarial taint, is chosen, and is injected with a stock vaccine five hours before the transfusion.

4. Blood to a quantity of 500 c.cm. is taken and is defibrinated, *for sodium citrate inhibits the bactericidal powers of blood.*
5. The defibrinated blood is given intravenously in the usual manner.
6. The dose is repeated if necessary.

According to other observers, transfusion with ordinary citrated blood is equally efficacious.

MILIARY TUBERCULOSIS

General Considerations

Massive tuberculous invasion of the blood-stream does not as a rule occur unless the resistance of the patient has been previously greatly lowered, or unless a large dose of tubercle bacilli is quickly disseminated into the circulation. The former condition holds towards the end of a chronic and protracted pulmonary tuberculosis, or in children after a severe attack of measles or pertussis, and the latter occurs when the rapid local caseation of a tuberculous lesion is adjacent to an area rich in blood-vessels. That tubercle bacilli have been found in the blood of tuberculous patients and of inoculated animals is a proved fact, but that the organisms proliferate in the blood-stream at a rate similar to that of pyogenic cocci is very doubtful. The probability is that the blood in such cases is more or less constantly receiving fresh numbers of bacilli from some suitably situated focus and is distributing these indiscriminately over the body, producing in most organs the characteristic miliary tubercles.

Wright's (3) experiments suggest two ways in which the tubercle bacillus differs from the pyogenic organisms with regard to its growth in the blood-stream: first, individual bacilli proliferate in twenty-four hours to a number of 4–5, whereas individual cocci form colonies of many hundreds; second, the blood of tuberculous patients is more bactericidal, whereas that of patients suffering from streptococcal septicaemia is less bactericidal than normal.

These differences may be borne in mind when considering

the possibility of proving the presence of tubercle bacilli in the blood-stream of a patient. Numerous continental and American workers claim to have isolated the bacillus; their methods have been guided by three principles. Enough blood must be taken (20–40 c.cm.); the blood-cells are laked and the sediment is concentrated; this deposit is injected into a guinea-pig. No routine pathological method of this kind is in general use at present.

Pathological Findings

The common pathological findings in miliary tuberculosis are:

I. Leucopenia.
II. Lymphocytosis.
III. Anaemia.
IV. The presence of Bacilli in the Sputum, Urine, and Faeces.

Leucopenia

The white count in generalized tuberculosis is influenced by two main factors. As a rule, where the infection is relatively pure, as when it arises from the rapid caseation of some lymphatic gland, there is a leucopenia. This diminution affects chiefly the polymorphonuclear cells and to a lesser extent the lymphocytes. In severe cases the white count may fall even to below 1,000 per c.mm. Such cases are not common, and when seen early give a picture similar to that of typhoid fever by reason of the continued fever, splenomegaly, and leucopenia.

The two factors that prevent the development of this leucopenia are, first, the tuberculous inflammation of some serous membrane such as the meninges, pleura, pericardium, or peritoneum; secondly, when the infection has originated from a chronic pulmonary lesion, the presence of a secondary local pyogenic infection. In either case a leucocytosis generally results.

Lymphocytosis

In less acute forms of the disease, although the polymorphonuclear count is capricious, being increased or

decreased according to the presence of other factors, the lymphocytes are frequently increased in actual numbers. A polymorphonuclear leucopenia, provided the total count is thereby reduced below normal, will throw this actual lymphocytosis into relief so that the percentage figure is increased to an even greater degree.

Anaemia

In miliary tuberculosis a mild degree of anaemia is not uncommon. Since, however, the fluid content of the body is also often reduced, the deficiency in the red blood-cells is thus frequently masked. Sometimes the haemoglobin is found to be diminished to a greater extent than is the total red blood-cell count. The degree of such an anaemia frequently runs parallel with the seriousness of the prognosis.

Bacilli in the Faeces

Work by Calmette (4) has proved that in generalized tuberculosis considerable numbers of tubercle bacilli are eliminated into the bile in calves. There is no reason to suppose that the same is not true of human beings. An examination of the faeces therefore, preferably by a concentration method, is a reasonable procedure in cases of suspected miliary tuberculosis.

The tuberculin and the Pirquet reactions are usually negative in miliary tuberculosis.

Bacilli in the Urine

One of the normal functions of the kidney appears to be the elimination in the urine of any organisms that may gain access to the blood, in addition to the excretion of other materials.

In miliary tuberculosis search for tubercle bacilli by concentrating a twenty-four hours' specimen may occasionally give positive results. The centrifugalized deposit can be examined microscopically or can be injected into a guinea-pig. In the former case careful differentiation should be made from the smegma bacillus. The presence of this can be avoided by taking catheter specimens.

MALARIA

General Considerations

Malaria is essentially a parasitic disease of the red blood corpuscles. Although a transient passage through the serum is necessary to the organism in its form of sporozoite in order to reach fresh blood-cells, it is in the body of the latter that it proliferates.

Inoculation by the mosquito precedes symptoms by about twelve days. This delay is partially due to the fact that until the sporulating parasites reach a certain number no symptoms occur, and their generation is a very considerably slower process than is the continuous simple fission of bacteria.

The periodicity of symptoms depends upon the act of sporulation, for it is generally considered that simultaneously with the disintegration of the cell and the spilling out from it of the *merozoites*, toxin escapes into the general circulation. In benign tertian and quartan this periodicity is marked, but in subtertian sporulation is completely irregular.

The symptoms are thus, in benign tertian and in quartan, chiefly due to two causes, the presence of the parasite and the destruction of red blood-cells. But in subtertian the parasite becomes aggregated in great numbers in one organ, such as the spleen, liver, brain, or intestine, and by its mechanical presence in the last two sites causes grave symptoms.

The anaemia is produced by direct disintegration of cells by the parasite and possibly also by an indirect toxic effect upon the blood-cells or upon the erythropoietic tissues.

Pathological Findings in Malaria

I. Presence of the Organism in the Blood.
II. Anaemia.
III. Mononucleosis.
IV. Leucopenia.

Presence of the Organism in the Blood

The organism is found in blood smears taken from the peripheral circulation.

Two different smears are made, one in the usual way, as

if intended for a differential blood-count, which indeed is the case, and the other is made in the form of a thick smear. The object of the thick smear is that the pathologist shall, by adding distilled water to it, lake most of the erythrocytes. The parasites, which are not affected, are then stained by a Romanowski method. In cases where these are few in number the chances of finding them are obviously better in the larger quantity of blood. The thick smear is made by collecting upon the centre of the slide a fairly thick drop of blood, perhaps half an inch in transverse diameter. The edges of this are pulled out to some extent by a needle to flatten the drop, and this is allowed to dry before it is sent off. The fact that the quantity must be such as to allow of easy drying will prevent too thick a specimen from being made.

The pathologist will examine both smears, using the first for a differential white blood count and for an examination for parasites, and the second for the latter purpose only, if none are found in the first specimen.

If the parasite is not found in the blood the reason may be one of several:

1. It may not have been thoroughly searched for.
   The smear sent should be completely and comprehensively examined. Sometimes one or two parasites only are found upon a whole slide.
2. The patient may have been taking quinine.
   Quinine even in small doses will in some cases clear the peripheral blood of parasites.
3. The blood may have been taken at the wrong time.

In benign tertian and quartan the smear should be taken during a rigor to show ring forms, and just before to show adult parasites. The *gametocytes* may be found in small numbers at any time.

In subtertian malaria (aestivo-autumnal or malignant) the small ring forms, and then in small numbers only, are normally found in the peripheral blood during the febrile period. Subtertian *schizonts* only appear a few hours before death. Their appearance, besides being alarming, is important, for energetic quinine treatment may still save

the patient's life. Disappearance of the subtertian rings from the blood occurs more readily than does that of tertian rings after the exhibition of quinine. But much more prolonged and thorough treatment than this is needed to effect a cure or to render the patient no longer a source of infection to others. A further valuable criterion for distinguishing benign tertian from subtertian is a second examination eight to twelve hours after the first discovery of small ring forms. By that time the parasites of benign tertian will have further developed, while those of subtertian are individually unaltered.

4. The disease may be of the chronic variety.

In acute malaria the parasite is found in the blood in nearly 100 per cent. of cases, provided search is adequate (up to 2–3 examinations).

The number of parasites is proportional as a rule to the acuteness and severity of the attack, and as the disease advances or wanes in severity so the number of parasites fluctuates.

Briefly put, three negative examinations in an acute febrile illness exclude malaria; in a chronic one this does not hold. A positive result of course proves that the patient is infected. It must be remembered in malarial districts that the parasite is frequently present without producing symptoms, and that although parasites are found, the cause of the fever and illness may have to be sought elsewhere, but this does not occur in temperate climates. When three years have elapsed from possible exposure to infection the diagnosis of malaria can be regarded as unlikely.

Anaemia

The anaemia of malaria affects nearly equally the haemoglobin and the red blood corpuscles. The former is as a rule slightly the more deficient, giving a colour index of a little less than 1.

The red cells number about 3,500,000 to 4,000,000 in an established case of benign tertian, but this figure is the balance eventually struck between the powers of blood destruction by the disease and regeneration by the patient.

The first few paroxysms are especially destructive, the cell count falling by as much as 1,000,000 in a few days. Later immunity develops and the fall is arrested or even partially retrieved. Occasionally in severe continued infections a blood-picture similar to that of pernicious anaemia may occur. In subtertian malaria the anaemia is more severe, figures of 2,000,000 being common. Polychromatophilia and basophilia are common, but anisocytosis and poikilocytosis are rare in malarial anaemias.

Mononucleosis

There is in the disease an actual and a relative increase in the numbers of the large mononuclear leucocytes. Their percentage not infrequently reaches fifteen or more and their actual numbers 600 or more per cubic millimetre. The increase may persist for as long as three months after quinine has kept the blood free from parasites. It is often abolished at the actual time of the rigor and is most marked in the interval or when the disease has become chronic.

A further diagnostic point of great value is that these cells are often found to contain the melanic pigment set free by the sporulation of the parasites. Such intracellular pigment is very strongly suggestive of active malaria, even when parasites are not found.

Leucopenia

There is usually a leucopenia in all forms of malaria, the figure of 4,000 being an average finding. During the actual paroxysm the figure may rise to the normal only to fall again at its termination. Leucocytosis does not occur in any form of the disease unless as a result of some pyogenic or other dissociated cause.

The Pre-Blackwater State

The subtertian form is that which is associated with blackwater fever and the so-called pre-blackwater state. The latter condition is characterized by fever, enlargement of the liver, and icterus, and the chief finding in it, besides the usual presence of the subtertian parasite, is a very well marked urobilinuria.

SEPTIC OR MALIGNANT ENDOCARDITIS

General Considerations

Malignant endocarditis (5) is a typical septicaemia. Deep-seated infection occurs, its position being the heart valve; there is no chance of drainage and the enclosed infection spreads to the blood-stream; finally, as a result of continued attack the defence breaks down and the organisms proliferate in the blood.

The pathological stages are thus logical and definite.

In the acute cases infarction of various organs, such as spleen and kidneys, adds to the number of foci of infection, and renders their extirpation even more hopeless than was at first the case.

There would appear to be no structure more remote from danger of infection from the exterior than a heart valve, and various reasons have been suggested to explain how this may occur. It is held that previous damage to the valve by rheumatism or syphilis renders this structure easily vulnerable to organisms present in the blood-stream. Recent work, notably that of Starling (6), suggests that such is not invariably the case.

Gross (7) in his monograph emphasizes a factor that may in some cases be a determining one. He has shown that the cardiac valves, notably the septal cusp of the mitral valve, tend in certain individuals to retain their foetal vascularity throughout life; further, that this vascularity is seen frequently in cases of malignant endocarditis, the vascular cusp being most often the infected cusp. Gross states that he has never failed to demonstrate this vascularity in the infected cusp of malignant endocarditis.

Another condition where some local structural alteration may favour the origin of secondary bacterial infection is congenital heart disease.

The sequence of events is probably as follows:

Organisms present by chance in the blood-stream are carried round and ultimately lodge in a small arteriole terminating in a valve cusp. Here, owing to the absence of local tissue that can react by protective inflammation

against the invader, the organism grows. The cusp soon ulcerates; clot, consisting largely of platelets, is deposited upon the open area; organisms grow out into the clot, reach the surface, and are washed off into the blood-stream. Two sequels occur: firstly, portions of infected clot may get detached and be carried off to form septic infarcts and fresh nidi of infection in various organs; secondly, the continuous invasion of the blood ultimately renders this fluid no longer able to inhibit the growth of organisms in itself.

The clinical type of the disease varies according to the causative organism. Two main divisions, Acute and Chronic, are recognized.

The Acute cases are caused most commonly by

the *Streptococcus pyogenes*,
the *Pneumococcus*,
the *Staphylococcus*, and
the *Gonococcus*;

the Chronic cases by the streptococci, *salivarius* and *faecalis* (95 per cent.), and by the *Influenza bacillus*.

There is in the acute cases generally some septic focus to be found whence the infection arose, such as a cutaneous abscess, a urethral discharge, a resolving pneumonia; but in the chronic type no obvious point of origin presents itself. The fact that the organisms in question are normal inhabitants of the mouth and the gut would suggest that the essential change is one rather of the patient's general powers of resistance.

Pathological Findings

I. Bacteriaemia.
II. Bacteriuria.
III. Secondary Anaemia.
IV. Leucocytosis.
V. Haematuria.

Bacteriaemia

In malignant endocarditis the blood is generally heavily infected. Libman (8) states that over 90 per cent. have a

positive blood-culture in the active stage of the disease if proper methods are used.[1]

Occasionally cases occur that seem to have remissions, losing their fever and their other symptoms. During such a period the blood becomes sterile.

It must be remembered that organisms such as the *Influenza bacillus*, the *Gonococcus*, and even the *Pneumococcus* are delicate, and require considerable care for their successful isolation from the blood, so that in a case presenting three of the classical phenomena of septic endocarditis, fever, a cardiac lesion, and signs of infarction, the fourth, a positive blood-culture, should be repeatedly sought in order to establish the diagnosis.

Bacteriuria

Careful bacteriological examination of a catheter specimen of urine may result in the isolation of an organism when the blood-culture remains sterile. If it be sent to a pathologist with a specimen of blood-serum, the complement-fixation test will very possibly prove its guilt or innocence should it be a streptococcus. The blood in malignant endocarditis contains antibodies to the homologous streptococcus to a high titre (9).

Secondary Anaemia [2]

This is generally present. It is of the chlorotic type, and this distinguishes the disease from pernicious anaemia. In the latter condition, fever, slight splenic enlargement, petechiae, and a systolic murmur at the apex of the heart are all sometimes to be found, but the type of anaemia is distinctive and its degree more severe; moreover, blood-cultures are persistently negative and a leucopenia is present.

Leucocytosis [3]

This is generally to be found in malignant endocarditis. A usual figure in the chronic cases is 12,000, but in the acute cases higher figures occur. The eosinophiles are almost invariably decreased in number.

[1] See the section on ' Septicaemia ', p. 5.

[2] See p. 114.

[3] See p. 7.

Haematuria

This is common, but not invariable. It is the result generally of infarction of the kidneys.

Where microscopical examination of a catheter specimen of urine shows the presence of red blood-cells in a patient with fever and a cardiac lesion malignant endocarditis must be strongly suspected. In such a urine a few casts, composed of red corpuscles or even epithelial cells, may be found.

Diagnosis

The diagnosis is established by the presence of a positive blood-culture in a patient with fever, a cardiac lesion, and signs of infarction.

The diagnosis is probable when these three coexist in a patient whose blood-serum contains complement-fixing antibodies to a high titre against an organism obtained from urine.

A leucocytosis is usual, but a leucopenia does not negative the diagnosis.

The absence of red cells from the urine does not negative the diagnosis.

Prognosis

The disease is almost invariably fatal. The end is to be expected sooner in the presence of

1. A heavy blood infection.
2. Signs of infarction, such as haematuria, and frequent attacks of transient pleurisy in the rare cases of pure right-sided infection.

Treatment

The slow rate of progress of the chronic cases allows of the possibility of immunizing relatives or an animal against the isolated organism. From these sources antiserum can be prepared and given, or in the case of the relatives transfusions of immunized blood can be tried.

Such forms of treatment are generally of no avail, but they seem to hold out the greatest promise of success, especially if an early diagnosis can be made.

Vaccines and stock sera are of no use.

LOBAR PNEUMONIA

General Considerations

Lobar pneumonia can most logically be considered as a generalized blood infection with an incidence upon the lungs. The causative organism is generally the pneumococcus. It is transferred from mouth to mouth by coughing, sneezing, and by direct contact, and in certain cases, as among the South African miners, has caused severe epidemics. If the recipient of the organism is susceptible it appears to spread down into the trachea and thence outwards into one or more lobes; the blood may be invaded before definite pulmonary physical signs appear. Thus pneumonia is an infective disease, transferred through cases, and probably to a far larger extent through carriers, and attacking only those who happen temporarily to be susceptible.

A clear understanding of its bacteriology is dependent upon recognition of the division of the pneumococci into four serological types. The identity of these types was first worked out independently by Dochez and Gillespie (10) in America, and Lister (11) in South Africa in 1913.

Whereas broncho-pneumonias have as their predominant pneumococcus a Type IV in about 70 per cent. of cases, lobar pneumonias have a Type I in nearly 50 per cent. and a Type II in about 20 per cent. of cases. Type III is a particularly virulent and fortunately a very uncommon organism. These percentages vary slightly according to differences of country, season, and epidemic.

Blood-Infection

Having reached the blood-stream the organism is present there in smaller or greater numbers throughout the disease. The number of organisms appears to be greatest on or about the fifth day, as measured by the percentage of positive cultures on different days. But where in addition to the pulmonary consolidation some additional focus is present, such as an acute otitis, a pericarditis, or an acute empyema, the blood infection becomes heavier; further-

more in fatal cases the number of organisms increases greatly during the few days directly antecedent to death.

Statistics with regard to the percentage of cases of pneumonia in which the blood-culture is positive vary according to the technique. The chief point appears to be the necessity of diluting the blood sufficiently (12) with the nutrient medium. Kinsey's (13) first twenty-five cases were diluted one in six, and his second twenty-five cases one in fifteen; 12 per cent. of the first group and 76 per cent. of the second were positive. A further point is that cultures should be incubated for a week (14) in order to exclude a light infection, though growth usually appears within twenty-four hours. A negative blood-culture throughout indicates a 90 per cent. chance of recovery. A strongly infected blood-culture on the seventh day and later suggests a fatal prognosis.

Lung Infection

The pneumococcus is widely spread throughout the affected lobes from the first day of the disease. In cases that recover, organisms generally become unobtainable after the fifth or sixth day, whereas in cases ending fatally they become locally more and more numerous (15).

The bacteriology of the sputum generally runs to some degree parallel with the lung condition, but organisms persist much longer, owing probably to the persistence of secondary bronchitis.

Pathological Findings in Pneumonia

I. Leucocytosis.
II. Presence of Pneumococci in Blood,
,, ,, Sputum,
,, ,, Lung juice,
,, ,, Urine.

Leucocytosis

Lobar pneumonia is almost without exception accompanied by a large polymorphonuclear leucocytosis. This is present within a few hours of the onset of the disease and persists until its termination. The average figure in adults

is in the neighbourhood of 25,000 per c.mm., in children rather higher. A count of 30,000 or even 40,000 is not uncommon in a severe case, and the number appears to be directly proportional to the vigour of the patient's reaction against the infection. Where the severity of the infection is overwhelming little or no increase may occur. A falling white count with no clinical improvement is of bad omen.

The eosinophiles vanish from the blood-stream during the disease.

A series of white counts during the progress of a pneumonia, when taken in conjunction with the clinical findings, may give valuable information as to the progress of the disease.

The chief value, however, of the leucocytosis of lobar pneumonia is seen in diagnosis.

In children sudden abdominal pain frequently occurs as an early sign of appendicitis, of acute pleurisy or pericarditis, and of lobar pneumonia; in the differential diagnosis between the first and the last of these conditions the white count is of considerable value. In 90 per cent. of cases of lobar pneumonia in children the count is above 15,000, and in 90 per cent. of cases of appendicitis uncomplicated by abscess or peritonitis the count is below 15,000 (16). The higher the count the more probable is pneumonia.

A second type of case where a white count is of value in diagnosis is acute massive pulmonary tuberculosis. This in the rapidity of its onset, in the degree of its fever, and in its pulmonary physical signs may sometimes closely simulate pneumonia. In such a case the leucocytosis, if any, might be small. Such a result should hint at the possibility of some condition other than lobar pneumonia.

The Presence of Pneumococci in the Blood

Allusion has already been made to the septicaemic nature of lobar pneumonia. This bacteriaemia is of practical importance for two reasons, prognosis and treatment. Careful blood-culture on or about the fifth day of the disease gives the highest number of positive results. The mortality in cases with a positive blood-culture is much higher than those

with a negative one; the Rockefeller workers in a series of 448 cases had a death-rate in Type I infections, with a positive blood-culture, of 26 per cent.,[1] in Type II of 73 per cent., Type III of 100 per cent., and Type IV of 52 per cent.

Several different observers give a mortality of about 8 per cent. in cases with a negative blood-culture. A negative result is thus of considerable value in prognosis. As the disease progresses the number of positive blood-cultures in cases that recover becomes less as the crisis is neared. A positive result late in the disease is of bad omen.

A positive blood-culture early in the disease may be of some therapeutic value, if sputum is not obtainable, for successful serum treatment depends upon early isolation and typing of the causative organism.

The Presence of Pneumococci in the Sputum

The sputum is the most constant early source whence the pneumococcus can be obtained, but in order that the result may be as satisfactory as possible certain precautions should be observed.

Sputum should be collected as early in the disease as is possible, for the success of serum treatment depends entirely upon speed. The earlier serum is given the lower is the mortality.

The patient should be asked to wash out the mouth with boiled water once or twice; he should then expectorate into a sterile jar, pot, or test-tube. Coughing and sputum can often be evoked by rolling the patient over towards his sound side. The specimen should be sent immediately by messenger to the pathologist, who has been already warned. In this way the organism can be typed within sixteen hours or even less.

A 'rusty' specimen should be chosen if possible.

The pathologist uses the precipitin test or the agglutination reaction.

It is obvious that the most serious loss of time occurs in the transference of the sputum from the patient to the pathologist and in the obtaining by him of a pure culture

[1] These cases were treated with serum.

of the organism. That no time may be wasted by this process it is essential that as sterile a specimen of sputum be obtained as is possible in the first place.

The Presence of Pneumococci in the Lung

Lung Puncture. In some cases where sputum is difficult or impossible to obtain, as is sometimes the case in children, the causative organism can be obtained direct from the pneumonic lung by lung puncture. A record syringe is used and the needle is of medium size (No. 18 or 20). About 0·5 c.cm. of sterile saline is aspirated into the sterile syringe. The skin is cleaned with every possible care over the solid lobe, which is then explored to a depth of about one and a half or two inches. The saline is slowly expelled into the lung and suction is commenced. A few drops of blood-stained 'juice' are obtained which should be sown direct, by the bed-side, on to a blood agar or other suitable plate.

Lung puncture by a number of different observers, including Clough (17), Lyon (18), Rosenow (19), &c., gave positive results in about 50 per cent. of cases in adults, and in children 60 to 70 per cent.

It is obvious that the method is bacteriologically a very clean one.

The Presence of Pneumococci in the Urine

Pneumococci are not infrequently present in the urine during an attack, and can be isolated by culture of a catheter specimen in blood-broth.

SERUM TREATMENT IN LOBAR PNEUMONIA

Neufeld and Handel (20) in 1910 first used Type I antiserum in pneumonia and Cole in 1915 produced serum against Types I and II. Since then a number of observers have employed serum treatment, and the majority claim that the mortality in treated cases is lower than in those untreated. Serum successfully protects mice when infected with what would otherwise be many times a lethal dose of live pneumococci.

It is of importance that if serum is used it should be employed as early as possible in the disease, and its value

in treatment decreases rapidly day by day after the third day.

Indications for serum treatment are, that the diagnosis has been made on the first, second, or third day of the disease, that the organisms can be rapidly typed, that the patient is an adult—for practically every child under 15 years of age recovers in any case from true lobar pneumonia—and that serum can be given in sufficient amount before the fifth day of the disease.

If so administered it in some cases aborts the attack, and in others appears to reduce its length by a day or two. In any case it is a form of treatment practically devoid of risk and one whose value is founded upon definite experimental and clinical evidence.

Serum is of proved value only in Type I infections; it is of probable value in treating Type II, and of no value at all in dealing with Types III and IV.

Dosage. Three doses should be given at intervals of eight hours.

It is a waste of serum and of energy to give an insufficient amount. The total dosage should be about 250 c.cm. in all for an adult. The first two doses should be in the neighbourhood of 100 c.cm. each and the serum should be added to an equal quantity of sterile saline to diminish the viscosity. Administration should be slow, and can be by gravity or by a transfusion flask. In order to avoid the rare accident of anaphylactic shock a preliminary intradermal injection of 0·1 c.cm. of serum should be made to reveal hypersensitivity. Should this be found, desensitization can be attempted.

Vaccine Treatment in Lobar Pneumonia

Vaccine treatment is urged in lobar pneumonia by certain observers. The most convincing case is that made out by Wynn (21). His view is that, whereas the danger of giving vaccine so as to produce a negative phase is a very real one when an infection is subacute or chronic, in a disease as acute as lobar pneumonia the patient will have had no time in which to become sensitive to the foreign protein of the pneumococcus. Thus it is not only safe but desirable

to give quite large doses of vaccine upon the first, second, or third day of the disease. The vaccine he uses is a stock one made from mixed strains of virulent primary growths of pneumococci, and the doses are 'at least 100 millions' for an adult, and for a child aged 12 half as much.

The important point is to give the first dose at the earliest possible moment after the onset. Of his series of 100 patients, 83 per cent. had a normal temperature in twenty-four and 100 per cent. in forty-eight hours, if the subcutaneous injection were given on the first day of the disease. If it were given on the second, 57 per cent. had a normal temperature in twenty-four, 93 per cent. in forty-eight, and 100 per cent. in seventy-two hours. This result is apparently due to the earlier production by the body of antibodies which neutralize the pneumococcus toxin early and before the heart or nervous system have become severely involved.

Failure of the treatment, when it is instituted later in the disease, is to be expected; for by that time the production of toxin is much greater, and its fixation in vital tissues has already occurred.

TYPHOID FEVER

General Considerations

Typhoid fever is an infection due to a specific organism, the *Bacillus typhosus*. Pathologically it must be considered as a septicaemia, which slowly disappears as a definite localization of the disease is established in the intestine. In addition, a focal pyogenic reaction against the bacillus may occur in a variety of places, either during the disease or at an interval of time after its subsidence.

For the first few days of the illness, or indeed of a relapse, the organism occurs in considerable numbers in the blood-stream. It is sometimes still present in smaller numbers up to the end of the first week, but after then is generally not found. By that time, however, the blood has begun to form antibodies, among them agglutinins, and by the end of seven days these are usually present in demonstrable amount. In spite of the severity with which the disease

attacks the intestine, the bacillus does not occur early in the stools in any numbers. Later its occurrence becomes commoner. The function of the kidneys in typhoid, as in other septicaemias, is to excrete the organisms as well as waste products; thus the urine often contains typhoid bacilli at an earlier stage than do the stools. Their excretion, due frequently also to an infection of the urinary tract, may persist for many weeks.

Pathological Findings in Typhoid Fever

The chief pathological findings are:

I. The Presence of the Bacillus in the Blood.
II. The Presence of Agglutinins in the Blood.
III. Leucopenia.
IV. The Presence of the Bacillus in Urine and Stools.

The Presence of the Bacillus in the Blood

The organism may be expected in a blood-culture during the first few days of the disease, may be hoped for up to the end of the first week, and may be searched for up to the end of the second. The most successful method (22) would appear to be to withdraw 10–15 c.cm. of blood, to mix this with ox-bile, to incubate for twenty-four hours, and then to subculture on to agar or into broth. If a specimen be sent by hand from some distance to the laboratory, it is advised that a rubber cap be placed over the test-tube containing the blood and bile, and that this be placed in a thermos flask containing water at a temperature of 100° Fahrenheit. Blood-cultures done in the usual way in broth are worth doing in the absence of ox-bile, but are generally not positive in more than about 38 per cent. of cases. Absolute sterility of technique is essential.

The Presence of Agglutinins in the Blood

By the end of the first week of the disease agglutinins begin to appear in the blood. The simplest method of showing their presence is by using Dreyer's modification of Widal's test. About 2 c.cm. of blood will provide a sufficient quantity of serum. Varying dilutions of serum are

mixed with a standard emulsion of killed bacilli, and water is added to make the volumes equal in all tubes. Incubation at 55° C. for two hours will produce agglutination that may be easily recognized with the naked eye.

Normal serum does not show the presence of agglutinins above a dilution of 1/25, but a previous attack of typhoid fever or a previous inoculation with a T.A.B. vaccine will account for their presence after an interval of even two or three years. If, therefore, agglutination occurs during a febrile attack in a patient who may have had typhoid, or has been inoculated against it, some years previously, the test should be repeated after an interval of a few days.

A patient with early typhoid whose blood-serum agglutinates *B. typhosus* to a dilution of 1/50 on the fifth day of the disease will probably agglutinate to 1/250 on the tenth, whereas the agglutinins remaining after an old infection remain at the same level. The agglutinin content rises with the progress of the disease, and by the end of the third week has almost invariably reached a high titre. In the case of typhoid fever occurring in those previously vaccinated against it, this rise in the titre may be delayed even into the third week, but it eventually occurs. If agglutinins are present to a dilution of 1/50 it may be said that the patient either has or has had typhoid, or has been inoculated against it.

The blood should always be tested against *B. paratyphosus A* and *B*, as well as against *B. typhosus*, for by other means differentiation is often impossible, and where typhoid is suspected clinically paratyphoid may often be found. A negative agglutination result on the tenth day rules out typhoid in the very large majority of cases.

Leucopenia

A diminution in the polymorphonuclear cells is characteristic of uncomplicated attacks of typhoid fever. The leucopenia so produced seems to some extent to be proportional to the severity of the infection. The count may fall to 2,000 or even less. A case with a white count of 12,000 or over is unlikely to be one of uncomplicated typhoid fever.

If the count is over 15,000 that diagnosis is practically ruled out. Should perforation occur, the count may rise rapidly to 15,000 or more, but only for a short time, as it falls again with the development of peritonitis. Haemorrhage also is often followed by a transitory leucocytosis.

Presence of the Bacillus in Urine and Stools

Bacilluria occurs early in the disease; the organism can be isolated sometimes by the end of the first week, and infection of the urine may persist almost indefinitely.

The specimen is taken with all aseptic precautions and is incubated in bulk. Subcultures are made after twenty-four hours upon lactose litmus agar or some similar medium by which non-lactose fermenting organisms are easily differentiated.

The stools contain organisms at a rather later stage than does the urine. It is generally useless to examine them before the end of the second week. There are two sound indications for examination of the stools and urine for organisms of the typhoid group. Firstly, such examinations should be made as a routine after typhoid to prove that the convalescent patient has not become a carrier. Three negative results by a skilled bacteriologist are sufficient, provided the patient has been up and about on his feet during the collection of specimens. Secondly, there are a number of organisms closely allied to the paratyphoid bacilli, such as *B. aertrycke* and Gärtner's bacillus, that may give rise to symptoms not unlike a typical or an abortive attack of typhoid.

An agglutination test of the blood of a patient infected by one of these would be negative with the typhoid bacillus, though cross-agglutination with paratyphoid bacilli might occur, but the organism at fault might well be present in the stools or even urine; and the presence of a non-lactose fermenting motile bacillus would suggest the advisability of having the serum put up against this organism. (See also p. 191.)

CONCLUSIONS

Diagnosis

First week: Blood-culture in bile is positive in a high percentage of cases, in broth in about 38 per cent. of cases. (Incubation of cultures should persist for a week.) Leucopenia is present.

Second week: The agglutination test is positive and becomes more and more strongly so.

Leucopenia persists. Leucocytosis of 15,000 excludes typhoid.

Blood-culture in bile is still positive in a fair percentage of cases.

Urine culture may be positive.

Third week: Agglutination test more strongly positive.

Bacillus present in stools and in urine.

Prognosis

To some extent it is true that the more pronounced the leucopenia the severer is the infection. A return to their normal figure of the eosinophile cells is said to indicate a good prognosis. In the earlier stage of the disease they diminish in numbers.

Treatment

Vaccine or serum treatment is little used in the course of typhoid fever. But Rodet and Bonamour (23) record results in 246 cases of typhoid fever treated with a special serum prepared by the former. They found that the best results occurred when it was given early in the disease in the neighbourhood of the end of the first week. Their mortality rate was 11 per cent., and in cases treated before the twelfth day only 8·4 per cent. In a protracted case a vaccine may be tried, but the doses should be small. Five or ten millions would probably be sufficient for the first dose. Intervals between injections should be of six or seven days, and the doses should be doubled each time.

Another form of vaccine treatment which seems to be more in the nature of protein shock has been described. It consists of the intravenous injection of a stock typhoid emul-

sion in large doses. Fairley (24) in a full account advocates 120 millions as a first dose; this figure is increased gradually up to 200 millions; three or four doses are given in all. Comparing the results in twenty-nine cases, and comparing them with twenty-nine controls, he claims that the fever is shortened by ten days; the earlier in the disease the treatment is started the better will be the effect. He states that excessive reactions need not be feared.[1]

Prophylactic vaccination, on the other hand, is a measure of proved value. The vaccine used is a stock one and can be obtained from Burroughs Wellcome, Parke Davis & Co., and several other commercial firms. Two doses are given at an interval of seven to ten days. The first dose should contain 500 millions of *B. typhosus* and 250 millions each of *B. paratyphosus A* and *B.* The second dose contains twice these amounts. Protection is good and lasts in most cases for several years. Prophylaxis should be advised for individuals going to some country where the disease is prevalent. As a result of prophylactic inoculation the general reaction may be severe. Headache, malaise, shivering, and fever are the chief symptoms, and they may last for two or three days. More rarely the reaction simulates a mild attack of appendicitis and sometimes even of meningitis (25). Oral administration of prophylactic vaccine is under trial, especially in France, and promising results have been obtained.

Carriers of the *Bacillus typhosus*, whether in the urine or stools, should, if other measures fail, be treated with a vaccine. The commencing dose can be 50 millions and the subsequent doses doubled, at weekly intervals, to a maximum of 500 or even 1,000 millions.

Sequelae

The typhoid bacillus may cause localized lesions long after the primary attack. Periostitis of the sternum or ribs is not very uncommon. If pus or semi-purulent material be obtained by needle and syringe in such cases the bacillus can generally be cultivated direct. Arthritis and spondy-

[1] Compare Wynn, *Vaccine Treatment of Pneumonia.* (See p. 26.)

litis may follow typhoid; their true nature can be ascertained by an agglutination test.

Carriers may retain the organism in urine and faeces for years.

PARATYPHOID A AND B

All the statements made concerning typhoid fever apply with equal truth to both paratyphoid infections. The bacteriaemia, leucopenia, agglutinin content of the blood, and the presence of the organisms in the urine and stools, are all found equally in these diseases and at similar periods of the disease.

Infections by *B. aertrycke* and Gärtner's bacillus produce agglutinins in the blood as typhoid does. Leucopenia may also be present. The organisms are more readily obtained from the stools and at an earlier stage of the disease than in the typhoid infections.

UNDULANT FEVER

This disease bears a close clinical resemblance to typhoid fever. It is caused by the *Micrococcus melitensis*, infection being frequently milk-borne. Though commonest in the Mediterranean area it has been recorded in many other European and American countries. The disease is a septicaemia, the organ most affected being the spleen.

Diagnosis cannot usually be made by clinical means alone, although sometimes the periodic shape of the temperature chart and the associated arthritis produce a characteristic picture.

Pathological Findings

I. Presence of the Organism in the Blood.
II. Presence of the Organism in the Urine.
III. Presence of the Organism in Material obtained by Splenic Puncture.
IV. A Positive Melitene Reaction.
V. Presence of Agglutinins in the Blood.

The organism is present in the blood and can be obtained by blood culture during the height of the pyrexia in a

reasonable proportion of cases. The blood should be immediately inoculated into flasks, 5 c.cm. of blood to 50 c.cm. of broth per flask, and frequent subcultures made on to trypsinagar slopes. Incubation for at least ten days is essential. A negative result does not exclude the disease. The identity of an organism obtained is confirmed by agglutination against standard sera of known titre.

The organism should be looked for in cultures made from catheter specimens of urine.

Puncture of the spleen is not a method of diagnosis to be lightly undertaken. A positive result, however, has been obtained in cases where the procedure has been deemed justifiable.

A positive intradermal **melitene reaction** is definite and valuable evidence in favour of the diagnosis of undulant fever. A negative result, in a well-established case of pyrexia, makes the diagnosis unlikely.

Agglutination is valuable after the second week of fever if the result is positive. The serum is tested against several strains of *M. melitensis* and against *M. paramelitensis*. A negative result, owing to the variety of strains of the organism, is not exclusive.

Prognosis

Certain deductions have been drawn from variations in the agglutinin content of the blood.

Unfavourable signs are said to be a persistently low figure, a rapid fall from a high to a low figure, and a continually decreasing figure. Good signs are said to be a persistently high figure and a rising figure.

Treatment

Vaccines have been tried. Their use in the acute stage is contra-indicated. Sensitized vaccines are worthy of a trial in the chronic stage of the disease in doses of 100 millions and upwards.

Prophylactic treatment by the oral administration of vaccines is under trial.

CHAPTER II

METHODS OF INVESTIGATING FEVER OF UNCERTAIN ORIGIN

General Considerations

Continued fever[1] accompanies many diseases in adults, children, and infants; when the symptoms are equivocal and the physical signs indefinite a diagnosis may sometimes be facilitated by a correct interpretation of the pathological findings.

But the pathological laboratory should be used as a place which will return specific answers to specific questions, rather than as a temple to which the harried physician turns entreating arms in the extremity of his need. The man who when baffled demands a blood-culture, a complete blood-count, and every other test he can think of is as likely as not to receive answers to his questions that will only serve to lead him deeper into the mire of doubt.

MAJOR CONTINUED FEVERS

The commoner major continued fevers are: acute tuberculosis, septic endocarditis, typhoid and paratyphoid fever, acute rheumatism, lymphadenoma, malaria, and septic conditions; the commoner causes of low intermittent fever are chronic tuberculosis, chronic septic conditions, *Bacillus coli* infections, hyperthyroidism, and severe anaemia. In children and infants there are frequently found in addition otitis media and dyspepsia. Certain other conditions may be hidden, having fever as their only clinical manifestation; for example, liver diseases, such as neoplasm or amoebiasis, and syphilis.

Pathological Findings in Major Continued Fevers

By a major continued fever is meant a condition in which pyrexia to the extent of 102° or more is present for three weeks or longer.

[1] By continued fever is here meant pyrexia, both of a sustained and of a remittent type, and whose duration is one of three weeks or longer.

Signs and symptoms, though often very slight, generally are present in reference to one or other of the main organs or functional systems of the body. Bronchitis may be the dominant manifestation in any one of the group. Abdominal discomfort, with constipation or diarrhoea, produces an equally non-committal picture, though of course it suggests typhoid. Joint pains are not common during the first ten days of typhoid or in malaria, but are found in the others. Rigors are very rare in acute tuberculosis, acute rheumatism, and in typhoid, but may occur in all of the others. Severe sweating is commoner in acute rheumatism, acute tuberculosis, and septic endocarditis. Splenomegaly may be common to all. The possessor of an old mitral lesion is immune to none of the other conditions, but probably more susceptible to septic endocarditis than is a normal individual. The murmur present may be misleading. Delirium is commoner in typhoid fever, acute rheumatism, and septicaemia; the sufferer from acute tuberculosis, septic endocarditis, or lymphadenoma is generally mentally clear-headed.

The following Laboratory Investigations may give help in Diagnosis:

I. The Leucocyte Count.
II. Haemoglobin Estimation and Erythrocyte Count.
III. Blood-culture.
IV. Widal Reaction.
V. Examination for Cells and Organisms of:
    Urine
    Sputum.
    Joint Fluid.
    Stools.
VI. Biopsical Examination of a Lymphatic Gland.

Leucocyte Count

A leucopenia suggests typhoid fever or acute tuberculosis, but it may occur in lymphadenoma; it is rare in septic blood infections. A leucocytosis of about 12,000 nearly excludes typhoid fever, except when pleurisy or pericarditis

is present or just after haemorrhage, but is compatible with acute tuberculosis. It is about the usual figure in lymphadenoma, is rather low for septicaemia and for a severe attack of acute rheumatism or for the acute form of septic endocarditis. A white count of 20,000 excludes typhoid fever, is very unusual for acute tuberculosis, is high for lymphadenoma, is not uncommon in acute rheumatism with pericardial involvement, and is usual in septicaemia; with acute septic endocarditis it is compatible, but is a somewhat high figure.

Differential Count

The cell of most significance is the eosinophile. The eosinophiles are often present in normal numbers in acute tuberculosis and lymphadenoma; they are usually absent in septic endocarditis, septicaemia, early typhoid fever, and acute rheumatism. Their absence is of considerable value diagnostically, as is their return prognostically.

Haemoglobin Percentage and Red Cell Count

The haemoglobin percentage falls most rapidly in septicaemia; nearly as quickly in acute rheumatism and in severe typhoid fever; more slowly in septic endocarditis and in an average attack of typhoid fever; only slightly in lymphadenoma, and in some cases of acute tuberculosis not at all.

A positive blood-culture only is of value; a negative result is often reported even in the presence of bacteriaemia. The culture should be incubated for at least a week, and other precautions should be taken, as described under the headings of the individual diseases mentioned. A positive blood-culture may prove the presence of typhoid fever, septic endocarditis, and septicaemia. Repeatedly negative results are more common in septic endocarditis than in streptococcal or staphylococcal septicaemia. Pneumococcal, influenzal, and gonococcal septicaemia are often difficult to prove by blood-culture.

The Widal reaction is of value after ten days from the onset of the fever (see p. 28). Typhoid fever can then be excluded in the face of a negative result.

Examination of Urine and Sputum

The typhoid bacillus (p. 30), tubercle bacillus (p. 12), and the causative organism of a septicaemia (p. 6) may any one of them be recoverable from the urine or sputum.

Puncture of a joint containing fluid may prove the presence of a pyogenic organism, but even in a septicaemia with joint lesions the fluid is often sterile, though containing polymorphonuclear cells. The joint fluid of acute rheumatism contains many polymorphonuclear leucocytes and often much blood, but is sterile.

A complete examination of the stools is not often of value in a pyrexia of uncertain origin, but occasionally will yield information. An amoebic hepatic abscess may be the latent cause of continued fever, in which case cysts may be found; or a subphrenic abscess or a similar latent abdominal septic condition may be present, in which case, if there is any communication or propinquity with the gut, the greatly predominant organism in the film may be a streptococcus or some other unusually numerous inhabitant. Moreover, pus may be present.

The removal of a lymphatic gland is often the only way of making the diagnosis of lymphadenoma, and is always the only sure laboratory way. It should be remembered that lymphadenomatous tissue may be present in one enlarged gland and not in its neighbour, and that it may be present in one half of the gland and not in the other; that finally tuberculosis is not an uncommon lesion to find in glands which are definitely also lymphadenomatous, and that therefore, logically, one gland may show a tuberculous and the next one to it a lymphadenomatous picture, the latter being the disease which is causing the patient's symptoms. Thus a negative result does not exclude lymphadenoma, and a report proving the presence of tuberculosis does not exclude lymphadenoma. If possible two glands should be removed and sent entire to the pathologist.

Some stages of lymphadenoma are not easy to differentiate histologically, and a non-committal report, however disappointing, is sometimes the only honest one.

MINOR CONTINUED FEVERS

The commonest causes of minor continued fevers of uncertain origin and lasting for three weeks or more are, in adults, tuberculosis, septic endocarditis, Graves's disease, severe anaemias, *Bacillus coli* infections of the urinary tract, and septic foci such as a chronically inflamed appendix, gall-bladder, tooth socket, and occasionally prostate. Such fevers are generally remittent in type and frequently reach a height of less than 100°, though higher readings may be found.

The diagnosis must generally be made upon clinical grounds, but laboratory investigations are of some help. The white count is usually unchanged in tuberculosis, and eosinophiles are not infrequently present in the differential count in normal numbers; in septic endocarditis there is a leucocytosis and a diminution or an absence of eosinophiles; in Graves's disease the total white count is unchanged or slightly increased, eosinophiles are not usually diminished; the white blood count in anaemia will depend upon the type of the disease; in *B. coli* infections there is generally a moderate leucocytosis.

An anaemia is more characteristic of septic endocarditis, in which condition only, of those described, is a positive blood-culture to be expected. The presence of red blood-cells in the urine is common here also, though the presence in quantity of *B. coli* with them suggests this as being possibly the causative organism. The basal metabolism is increased in all febrile conditions.

A focal infection producing fever is generally accompanied by a polymorphonuclear leucocytosis and a diminution of the total eosinophile count. A slight chlorotic anaemia is usual. In the absence of fever a leucopenia with a slight actual lymphocytosis is not uncommon.

PERIODIC FEVERS

Certain fevers are characterized by regular remissions and recurrences. The commonest of them are malaria and lymphadenoma, and rarer examples are rat-bite fever, undulant fever, and relapsing fever. Trench fever was com-

mon during the Great War, but seems since to have disappeared. Acute tuberculosis in an adult and acute pyelitis due to the *Bacillus coli* in a child have both been observed by the writer in connexion with regular recurrence and disappearance of fever; in the latter case, fever appeared upon every other day for a week, and in the former the length of period and degree of fever were exactly analogous to that of a fourteen-day Pel-Ebstein chart for three cycles, after which the pyrexia became irregular.

Malaria, lymphadenoma, undulant fever, tuberculosis, and acute pyelitis have been dealt with elsewhere.

Rat-bite Fever

The history of being bitten by a rat, followed by a periodic fever, lymphadenitis, and rash, may give rise to the suspicion of rat-bite fever. The periods of pyrexia are regularly occurring and generally spaced at intervals of about five days. For a clinical description other sources of information should be consulted (26). The following laboratory findings are generally present.

Leucocytosis of a considerable degree is found during the febrile periods and disappears between them.

Blood-culture is sterile. Injection of the blood taken during the febrile period intraperitoneally into guinea-pigs may be followed after an incubation period of twenty-one days by transmission of the disease. In this event the demonstration of the motile organisms in a specimen of fresh blood is possible by dark-ground illumination. The disease is also transmissible by the juice of a punctured enlarged lymphatic gland.

The effect of intravenous arsenical treatment is striking, and a negative therapeutic result practically excludes the disease.

PYREXIA OF UNCERTAIN ORIGIN IN CHILDREN

Both infants and older children exhibit fever as a symptom more commonly than do adults. Two reasons for their greater instability of heat regulation are the large surface relative to body mass, and the immature co-ordinating

powers of the nervous system. Not infrequently this fever is accompanied by non-committal signs and symptoms.

Infants

Of the continued fevers mentioned as occurring in adults, lymphadenoma and septic endocarditis, except in gonococcal septicaemia, are both very rare in infants: typhoid fever, septicaemia, and acute tuberculosis may occasionally occur.

In all of these conditions the criteria are the same as those found in adults, with the important exception that any acute pyogenic infection in a young infant quite often fails to evoke a leucocytic response. This absence, even in the case of an acute osteomyelitis or septicaemia, is so striking as to be misleading to an observer who is unacquainted with the phenomenon, more particularly since the lack of response is often clinical as well as cytological.

The other causes of continued fever, physical signs being few or absent, found in infants, and giving a picture different from that found in adults, are most commonly inanition, acute otitis, or mastoiditis; less frequently tuberculosis or severe anaemia; rarely septicaemia.

The clinical pathological findings except in the case of the last are very subsidiary to clinical examination.

The presence of a polymorphonuclear leucocytosis is suggestive of a pyogenic condition. *Its absence is no argument against this*, as it is in older children and in adults.

Older Children

Children may suffer from any of the causes of major continued fever described above as occurring in adults. The clinical pathological findings are identical. Chronic tonsillar infection, *B. coli* urinary infections, tuberculosis, acute rheumatism, and disorders of assimilation are the more frequent additional causes of cryptogenic fever in older children. The degree of pyrexia in these conditions is generally less than in the first group.

In **tonsillitis** the diagnosis is made clinically.

B. coli **infections** are in the form of an acute pyelitis, a pyelonephritis, or a cystitis, either separate or in combina-

tion. The findings are identical with those described as occurring in adults (pp. 301, 314).

Tuberculosis, particularly of the mediastinal lymphatic glands, is an event of comparative frequency in children, and is often, though not always, accompanied by continued fever. There is frequently no physical connexion between the focus and the broncho-pulmonary surfaces, and the symptoms and pathological findings are therefore due to the absorption of toxins by the blood. Sputum is usually absent. The Pirquet test is positive.

A negative reaction in a child who has not recently had measles or pertussis, and who is not seriously ill, makes the presence of active tuberculosis very unlikely. A positive finding is of little value in a child above four years of age, as it may be due to past and arrested disease.

The blood shows generally a secondary anaemia of a mild chlorotic type. The white count is usually unchanged; a leucopenia may occur or there may be a slight leucocytosis, generally below 12,000. Lymphocytes are frequently present in larger numbers than normal. A normal white count, with a normal eosinophile count, is a point in favour of tuberculosis in a child of over two years of age who is suffering from continued fever.

Acute Rheumatism

In the earlier stages of acute rheumatism fever may be the most striking symptom. But there are few cases in children where the disease is not accompanied by definite cardiac dilatation or other cardiac or mild articular manifestations. The clinical pathological findings are a slight leucocytosis and a slight secondary anaemia of the chlorotic type.

Both of these give valuable aid in the assessment of the activity of the condition.

While the leucocytosis and the anaemia persist the process is probably still active. Any accentuation of either usually accompanies an advance, and any diminution a regression of the disease. Should the pericardium become widely involved a high leucocytosis and a fall in the haemo-

globin percentage generally follow, the first at an early and the latter at a slightly delayed stage.

Disorders of Assimilation

Occasionally children become febrile after the ingestion of certain articles of food. Brown bread and porridge, possibly by virtue of their mechanical irritative properties, sometimes have this effect. Rarely slight continued fever is coexistent in children with apparently perfect health. Pathological investigations will only be of help in suggesting these types of pyrexia by being normal in all respects.

CHAPTER III

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

General Considerations

Pathological changes in the meninges are manifested not only by fairly characteristic clinical signs, but by changes in the composition of the cerebro-spinal fluid, which are readily detected. This fluid is secreted by the choroid plexuses in the ventricles of the brain, escapes into the subarachnoid space through certain foramina in the roof of the fourth ventricle, and is absorbed into the blood through the arachnoid villi, finger-like processes of this membrane projecting into the venous sinuses, of which the Pacchionian bodies are the largest. The function of the fluid is purely mechanical; it serves to protect the brain, to allow of slight changes in volume of the brain tissue, and to receive waste products of cerebral activity carried to the subarachnoid space along the fine prolongations which accompany the cerebral blood-vessels.

To have available for examination a fluid which is so intimately associated with the pia mater and cerebral substance is to have an invaluable means of testing hypotheses suggested by clinical pictures in diseases of the central nervous system, and this is of especial help in certain infections of the meninges and cerebral substance. Cerebro-spinal fluid is as easily obtained by lumbar puncture as is pleural fluid by puncture of the thorax, and with proper technique the measure is equally harmless. It is an investigation which should never be omitted in any obscure case of central nervous system disease, or in any case presenting the symptoms of meningitis.

THE CHARACTERS OF NORMAL CEREBRO-SPINAL FLUID

Appearance, Amount, Pressure

Normal cerebro-spinal fluid is a sterile, colourless, isotonic saline fluid. Its appearance is not distinguishable from that of water. Its specific gravity is about 1005.

In a normal person fluid escapes from the puncture needle at a rate of about one drop in one or two seconds; the first $\frac{1}{2}$ to 1 c.cm. may escape more quickly, but the normal rate of flow is soon reached. When there is this indication that the cerebro-spinal fluid pressure is normal, it is not wise to remove more than about 5 c.cm., an amount sufficient for the more important investigations. Under pathological conditions, the amount of fluid which escapes through the puncture needle before the pressure becomes normal varies with the nature of the case. Provided no obstruction exists between the fluid in the skull and that in the vertebral canal, the higher the intracranial pressure the more fluid will be obtained.

It is possible to measure in millimetres of water the actual pressure of the cerebro-spinal fluid by a manometer attached to the lumbar puncture needle; a simple apparatus for the purpose has been devised by Greenfield, and is manufactured by the Holborn Surgical Instrument Company. The normal pressure in the horizontal position is from 60 to 150 mm. of water, but this is influenced to an appreciable extent by such factors as talking, crying, depth of breathing, and anaesthetic. Before reading the pressure one should see that pulse and respiration rates are normal. The amplitude of the oscillations of the fluid in the manometer are observed. Normally, compression of the jugular veins causes a rise in the cerebro-spinal fluid pressure; this is the Queckenstedt phenomenon, and is absent in a case of blockage of the spinal subarachnoid space, as also is an absence of the normal oscillations.

Chemical Constituents

Protein. Normal fluid shows a faint opalescence to the boiling test. The total protein averages 0·025 per cent. Globulin is present, but the amount is so small that a negative reaction is obtained with the usual tests, such as half saturation with ammonium sulphate.

Glucose. Glucose is present in normal fluid. The concentration is less than that in the blood, being from 0·048 to 0·085 gramme per cent. Fehling's solution is reduced,

though traces of another reducing substance contribute to this reaction.

Urea. Urea is present in normal fluid, the amount being 0·02 to 0·05 gramme per cent.; that is, the concentration is the same as normally exists in the blood.

Chlorides. The chloride content is very constant in normal cerebro-spinal fluid, being from 0·73 to 0·75 per cent. expressed as NaCl.

Cells

By the usual method of examination, namely, direct microscopical examination, it may be that no cells at all are demonstrable. At most a few lymphocytes only will be encountered, never more than 4 or 5 per c.mm., with perhaps one or two large endothelial cells derived from the lining of the subarachnoid space. Red blood-cells and polymorphs are never present in normal fluid, unless by accidental admixture during the operation of lumbar puncture. Any excess above this number is to be regarded as abnormal, though it does not necessarily indicate an infection of the central nervous system. Pleocytosis has been demonstrated, for instance, during the course of a great variety of acute infective fevers not associated with meningeal symptoms, such as lobar and broncho-pneumonia, influenza, scarlet fever, measles, variola, herpes zoster, typhoid fever.

If more than 5 cells per c.mm. are found, it is essential to determine their nature; this information greatly increases the value of a knowledge of the absolute count, as reference to the pathological findings in different infections of the central nervous system will demonstrate.

Blood in Cerebro-spinal Fluid

It is naturally important to decide whether blood present in any specimen is pathological, or is there merely as a result of lumbar puncture. Unless the blood is present in very large quantities, the following test is helpful: spin the fluid; if the supernatant fluid is colourless, the blood in all probability is the result of accidental bleeding during puncture. A yellowish supernatant fluid suggests patho-

logical bleeding. Van den Bergh's test for 'indirect' bilirubin is also useful; if blood has been present for some time in the theca a positive reaction will be obtained. A marked indirect van den Bergh reaction may be taken as indicating that blood has been in the theca certainly over twenty-four hours.

An investigation of the cerebro-spinal fluid for diagnostic purposes must vary with the clinical features of the case. For instance, if meningitis is suspected, investigation will proceed along somewhat different lines from those adopted when syphilis of the central nervous system is in question. If the fluid is sent to a clinical pathologist for examination, he should therefore be informed of the differential diagnosis which has been set up from clinical observations.

In the following account of the cerebro-spinal fluid changes in diseases of the central nervous system the figures given are mainly taken from Greenfield and Carmichael's monograph.

MENINGITIS AND MENINGISM

In an illness which begins suddenly with fever and a rigor, or a convulsion in a child, with intense headache which becomes worse as the illness progresses, where vomiting is an early symptom, and where after two or three days Kernig's sign appears and there is some pain and stiffness of the neck muscles, the probability that the case is one of meningitis is sufficiently strong to justify lumbar puncture. The differential diagnosis lies between (1) meningism, (2) acute otitis media, (3) so-called 'serous meningitis', (4) various forms of meningitis, including cerebral abscess arising from extension of infection from the bones of the skull, (5) acute poliomyelitis, (6) encephalitis lethargica, and (7) herpes.

Meningism is the term applied to the symptoms of meningeal irritation which are caused by toxaemia, and not by infection of the meninges. No changes occur in the cerebro-spinal fluid, beyond at most a slight increase in the protein content and occasionally a slight lymphocytosis. Such meningeal symptoms usually subside quickly. The commonest cause

is pneumonia in a child, but meningism may also arise during the course of other infective diseases in children, such as measles and mumps; while in adults it may occur in typhoid fever. In typhoid fever and pneumonia a diminished chloride content without pleocytosis is not indicative of meningitis. In mumps a condition which may be an actual infection with the virus of the disease is sometimes seen. The cerebro-spinal fluid shows a high lymphocytosis, an increased protein content, and a diminished chloride content.

On clinical grounds alone it may not be possible to decide between meningism and meningitis, though frequently the diagnosis will be strongly in favour of one or the other. Examination of the cerebro-spinal fluid will generally convert such probability into practical certainty.

Acute Otitis Media, without actual inflammation of the meninges, may give symptoms and signs so strongly suggestive of meningitis that an examination of the ears should be a routine in cases of meningeal irritation. The symptoms subside rapidly after puncture of the membrana tympani. It is in chronic inflammatory conditions of the middle ear that spread of infection to the meninges and cerebral substance may occur.

Serous Meningitis is a term applied to a sterile meningeal reaction common in children and associated with conditions such as acute otitis media and ethmoiditis. The signs and symptoms of a meningitis are present and the fluid shows increased pressure, a pleocytosis—chiefly lymphocytic—but no organisms. Recovery rapidly follows the clearing up of the primary condition.

CEREBRO-SPINAL FEVER

This is a widespread infection of the meninges, both of the brain and spinal cord, by the meningococcus. During epidemics it has been shown that this organism is present in the naso-pharynx not only in sufferers from the disease, but in many healthy people. These carriers are apparently immune to the disease, but play an important part in spreading the infection. The importance of carriers was fully demonstrated during the epidemics which occurred

among the forces during the Great War. It was found that overcrowding produced a high carrier rate, and that a rise in the carrier rate to over 20 per cent. preceded an outbreak of cerebro-spinal fever. Sporadic cases are always present with any carrier rate, but an epidemic is probably always preceded by such a warning rise.

There are two possible ways in which the meninges become infected. It may be from the naso-pharynx by direct spread along certain fine prolongations of the subarachnoid space which exist along the filaments of the olfactory nerves. Flack states that all cases of cerebro-spinal fever have meningococci present in the naso-pharynx in the earliest stages of the disease. In other cases infection may be by the blood-stream, a general meningococcal septicaemia being followed by localization of the infection to the meninges.

In its acutest form meningococcal septicaemia deals one of the most dramatic blows that can be struck at a healthy individual. In these cases, lasting for a period to be measured by hours, the blood-stream becomes rapidly and massively infected, purpuric spots and haemorrhage from mucous membranes follow, and death results. There has been no time for any localization to occur, and the post-mortem examination gives the findings of a severe septicaemia without meningitis.

In cases where the resistance is higher, although the blood-stream becomes infected early, meningeal inflammation also occurs; and to the rash, purpuric or erythematous —whence the disease derives its popular name of 'spotted fever'—are superadded definite meningeal symptoms and signs.

The Chief Pathological Findings in Cerebro-spinal Fever are :

I. Changes in the Cerebro-spinal Fluid.
II. Presence of the Meningococcus in the Naso-pharynx.
III. Blood—Leucocytosis and Presence of Meningococci.

The Cerebro-spinal Fluid escapes under greatly increased pressure ; 30 c.cm. is an average amount to obtain

before the flow from the puncture needle becomes of normal rate. In the very early stages it may be almost clear, but soon becomes turbid, and after a time may be definitely purulent. A clot forms on standing; early it may be web-like, but later is characteristically coarse. The cell count is greatly increased; hundreds or thousands of cells per cubic millimetre may be found. Examination in the early stages shows that the very great majority of these are polymorphonuclear leucocytes. It is usually possible to demonstrate the meningococcus in a film of the centrifugalized deposit, stained by Gram's method; the search may be somewhat laborious; as often the organism is found in small numbers only. When demonstration of the meningococcus by film preparations is unsuccessful, it may sometimes be obtained by culture, if suitable methods are employed. Cultures should be made at the bed-side on to a medium containing blood, and immediately placed out of the cold. A rubber-capped blood-legumen-agar slope can be inoculated, placed in a thermos flask containing water at 100° Fahrenheit, and sent by special messenger to the pathologist. If the cerebro-spinal fluid be sent direct, similar precautions respecting temperature should be taken.

If recovery is rapid, as is often the case after serum treatment, the polymorphonuclear cells soon diminish in numbers, leaving by the end of a week or ten days a practically normal fluid. If recovery is delayed the percentage of polymorphonuclears may slowly fall and that of lymphocytes rise. In some such cases the lymphocytes may be even more numerous than the polymorphs, which however persist to some extent throughout the course of the disease.

The protein content is increased, averaging 0·1 to 0·4 per cent.; a positive globulin reaction is obtained.

Glucose is diminished and may be absent.

Chlorides are diminished, figures from 0·65 to 0·68 per cent. being usually obtained.

The Naso-pharynx. The services of a skilled bacteriologist will be required in order to obtain evidence as to the presence or absence of the meningococcus in the naso-pharynx. He will obtain material by a post-nasal swab, and

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forthwith inoculate suitable media. The cultures will be carried back to the laboratory in a specially warmed container. Colonies of Gram-negative diplococci culturally resembling the meningococcus will be investigated further, their agglutination with known anti-meningococcal sera being determined. This is a difficult investigation, but may be of value in establishing a diagnosis when the organism cannot be found in the cerebro-spinal fluid.

The Blood. There is a considerable polymorphonuclear leucocytosis in all acute cases, with the exception of the fulminating meningococcal septicaemias, when a leucopenia may be found; total counts of 20,000 up to 50,000 are usual. A septicaemia is demonstrable in a large number of early cases, the organism being recoverable by blood culture and sometimes by direct examination of a blood film. In prolonged cases a progressive anaemia of the chlorotic type is seen.

The Serum Treatment of Cerebro-spinal Fever

Considerable advance in the serum treatment of cerebro-spinal fever was achieved by Dr. Mervyn Gordon's researches during the Great War. It was found for example that the value of a serum depended entirely upon its anti-endotoxin content, that is, on its power of protecting mice against the endotoxin of the meningococcus. Thus a standard was obtained for testing the therapeutic value of a given sample of serum. Further, the best results were obtained by the use of the serum corresponding to the type of meningococcus responsible in a particular case. As 80 per cent. of cases were found to be caused by meningococcus type I or type II, the routine procedure was to give a pooled serum of types I and II to every case until the type of infecting coccus could be determined, when the appropriate monotypical serum was given.

As in diphtheria, the earlier the serum is injected, the better are the patient's chances of recovery. The serum must be injected into the spinal theca through a lumbar puncture needle, after removal of at least an equal quantity of cerebro-spinal fluid. Injected by any other route it has

very little action, unless it be in the early stages when there is a meningococcal septicaemia. The serum should be warm, and the injection made very slowly by a record syringe. It is wise to give a general anaesthetic, as headache during injection is sometimes very severe. As a general rule, daily injections of 30 to 40 c.cm. should be continued until the fluid is clear or free from organisms, and the clinical signs of meningitis have subsided. Injections are of course repeated if a recrudescence occurs.

It is often difficult to decide whether to continue injections of serum or not; the most valuable guides are the presence of extra-cellular meningococci in the fluid and the clinical condition of the patient. Difficulty may arise because continued injection of serum may of itself lead to meningeal irritation, and cause large numbers of polymorphs to appear in the cerebro-spinal fluid. Thus after the meningococcal infection has subsided, the fluid may remain turbid from this 'serum meningitis'. In such cases meningococci are absent from the fluid, and glucose is present in approximately normal amount. It is important to realize the possibility of this condition, for the indication is to stop the administration of serum.

It is wise to give anti-meningococcal serum in all cases with meningeal signs and symptoms, whose cerebro-spinal fluid contains polymorphonuclear cells and is sterile.

Prognosis

It has been stated that the occurrence of serum sickness on about the twelfth day after serum administration—as shown by an urticarial rash with or without joint pains—is of good prognostic omen in this disease.

When organisms are present in a blood film most patients die within forty-eight hours.

When a blood-culture contains meningococci, the prognosis is generally bad. A negative blood culture has no prognostic value.

The bacterial content of the fluid corresponds to some extent with prognosis; a sterile fluid in an undoubted case is of good and a heavily infected one of bad omen.

MENINGITIS DUE TO OTHER PYOGENIC ORGANISMS, OR 'SEPTIC' MENINGITIS

This is almost always secondary to infection elsewhere in the body; for instance, middle-ear disease, acute inflammation of the nasal sinuses, septicaemia, and pyaemia.

The characters of the cerebro-spinal fluid are those found in the earliest stages of cerebro-spinal fever, except in regard to the nature of the organism. Usually the causal organism is demonstrable without difficulty. Pneumococci and streptococci are the most common causes of meningitis secondary to middle-ear disease or sinusitis. Staphylococcal meningitis may occur from the same cause, or as a complication of osteomyelitis or pyaemia. Meningitis due to Pfeiffer's bacillus as a complication of influenza, and meningitis complicating typhoid fever, where *B. typhosus* is recoverable from the cerebro-spinal fluid, are recognized conditions.

Examinations of the cerebro-spinal fluid should be the rule in all inflammatory conditions of the nasal sinuses or middle ear when symptoms of meningeal irritation persist in spite of local operative treatment. Turbid fluid may be obtained, indicating a meningitis either localized or generalized. The distinction is of some prognostic importance. The chloride content of the fluid is the most helpful investigation for this purpose; a diminution to 0·68 per cent. or less in a turbid fluid is evidence of generalized meningitis, while with a normal chloride content the infection may be localized. A clear sterile fluid in a case of this type suggests that the condition is to be classed as 'meningism', but such fluid may be obtained in very early stages of a true meningitis. If the cells are found to be increased, and the clinical symptoms do not abate, the puncture must be repeated.

Treatment and Prognosis

Most cases end fatally. Treatment is directed to the primary acute infection as well as to the meningitis; here the same principles which govern the treatment of cerebro-spinal fever are to be employed, namely, repeated lumbar punctures, and intrathecal injections of a specific anti-

serum, if one is obtainable. A gradual clearing of the fluid, from diminution in the leucocyte content, is a good prognostic sign.

TUBERCULOUS MENINGITIS

This may occur at any age, but is commonest in infants from two to five years. Although there are usually no characteristic symptoms or signs of tuberculosis elsewhere in the body, tuberculous meningitis is almost always secondary to a primary focus of infection. Autopsy reveals most often a caseating mediastinal or mesenteric gland. The general clinical picture of the disease is, in the majority of cases, a characteristic one. In the gradual onset, with a prodromal stage of peevishness, the comparatively mild pyrexia, and the frequency of ocular palsies in typical cases, it presents big differences from cerebro-spinal fever. Nevertheless, though a careful consideration of the whole clinical picture will often lead to a presumptive diagnosis, examination of the cerebro-spinal fluid should never be omitted; for a fluid showing the characters to be described will greatly strengthen the evidence for this diagnosis, and it becomes certain if tubercle bacilli can be demonstrated in the fluid. The tubercle bacillus can be found in the fluid in well over 50 per cent. of cases.

The characters of the cerebro-spinal fluid are these: It is a clear or slightly opalescent fluid under greatly increased pressure. On standing, a fine 'spider-web' clot forms. The number of cases where the tubercle bacillus is demonstrable would seem to vary with different observers, but all agree that positive results are obtained in the majority of cases, with proper technique and a sufficiently careful search. In the writer's experience, the best method is to attempt to demonstrate the bacillus in the clot. This is floated on to a glass slide, allowed to dry, and stained by the Ziehl-Neelsen method. Incubation of the clot *in situ* in the fluid for forty-eight hours as described by Canti (27) appears to be of advantage. The cells of the fluid are increased, averaging 100 to 300 per c.mm.; lymphocytes greatly predominate as a rule, but polymorphs may be present in large numbers, even up to 70 per cent.

The protein is increased; it may be only very slightly above the normal, but in other cases it is very definitely increased, 0·2 or 0·3 per cent. being not uncommon.

The globulin test is positive.

Sugar is diminished or absent.

Chlorides are diminished, being in the early stages 0·68 to 0·7 gramme per cent., and later 0·6 to 0·65 gramme per cent. or lower. This estimation is an important one; Greenfield states that a chloride content of 0·5 to 0·58 gramme per cent., though not commonly obtained, is pathognomonic of tuberculous meningitis.

The blood-count is of little or no value in diagnosis. There is a progressive secondary anaemia. In the early stages normal leucocyte figures are usual, but later a leucocytosis is the rule, figures of 10,000 to 15,000 or sometimes higher being found. A normal count may be suggestive when the diagnosis rests between tuberculous meningitis and meningitis due to one of the pyogenic organisms.

ACUTE POLIOMYELITIS

During the acute febrile onset of this disease, the symptoms may occasionally resemble those of cerebro-spinal fever, in that headache and vomiting, stiffness and pain in the neck and back muscles, with head retraction, Kernig's sign, delirium and stupor, occur. This meningitic type is not common.

An examination of the cerebro-spinal fluid will be undertaken in such a case, if the diagnosis is in doubt. In the early stages, even before paralysis, the cerebro-spinal fluid is always abnormal, the following being the characters usually found:

It is a clear fluid under high pressure.

The cells are increased, the total figures being very variable; anything from 10 to 600 or even more may be found. In the first few days polymorphs may predominate, but lymphocytes soon outnumber them.

The protein is slightly increased.

Glucose and chlorides are normal.

The cells diminish rapidly, and are usually normal after

the third week; the protein, however, tends to increase and may so remain for many weeks.

In fluids with a high protein content, a fine 'spider-web' clot may form on standing.

The Blood usually shows a polynuclear leucocytosis, total figures from 10,000 to 30,000 per c.mm. being found. The highest counts occur in the first week.

Treatment of Acute Poliomyelitis

The only form of specific therapy which may be of value is the administration of serum taken from a convalescent patient. In one who has recovered from the disease, the serum may possibly retain protective qualities for several years. During an epidemic it is not difficult to procure such convalescent serum. Its power to protect monkeys injected intracerebrally with the virus has been demonstrated by S. Flexner and P. A. Lewis (28).

Two hundred c.cm. of the donor's blood are collected in a sterile flask and the serum drawn off after the clot has separated. This is administered both intrathecally and intravenously on two successive days. If convalescent serum is not possible, horse serum may be used; this is stated to afford some protection against the virus. Serum treatment is of most value before paralysis has occurred, but its use is still reasonable during the first few days of paralysis.

ENCEPHALITIS LETHARGICA

Examination of the cerebro-spinal fluid in this disease will usually be undertaken in the early stages of atypical cases. The peculiar type of lethargy, insomnia, poverty of movement and rigidity, ocular palsies, and involuntary movements, are characteristic. But many cases do not show these common symptoms, and other diseases of the central nervous system will often come up for consideration before the diagnosis is established. Some cases, for instance, present the symptoms of an acute meningitis, and it is in these that an examination of the cerebro-spinal fluid will prove of most value. The meningitic type of acute poliomyelitis will be suggested in certain rare cases where spinal

nerve palsies occur. Though there is no characteristic feature of the cerebro-spinal fluid by which encephalitis lethargica can be recognized, several facts stand out as of paramount importance when the possibility of meningitis arises.

First, the cell count may be normal; and when cells are increased, they are found to consist entirely of lymphocytes. Polymorphs are never found, as they may be in any form of meningitis.

Secondly, a clot never forms in the fluid from encephalitis. Glucose is slightly increased, and the chloride content is normal. Excess of glucose is not peculiar to encephalitis, and cannot be regarded as a diagnostic sign.

The fluid is under increased pressure, and is clear and colourless. Increase of cells, if it occurs, is usually slight.

The total protein is normal, and the globulin tests negative.

Urine. Glycosuria may occur (see p. 328).

Blood. Changes in the blood are of little or no diagnostic value. There may be a slight diminution of red cells and haemoglobin. Leucocytes may be diminished, normal, or increased in numbers.

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

If neuro-syphilis always produced pathognomonic changes in the cerebro-spinal fluid, the physician would have a diagnostic test of the utmost value. Unfortunately, a positive Wassermann reaction in the cerebro-spinal fluid is the only certain sign, and syphilitic disease of the central nervous system may exist with a negative Wassermann reaction. However, by a consideration of the cell content of the fluid, the total protein and the globulin reaction, and Lange's colloidal gold reaction, with the clinical features of the case, the evidence of neuro-syphilis may be strong enough for practical purposes in spite of the absence of a positive Wassermann reaction.

Neuro-syphilis may so mimic other nervous diseases, that in any obscure nerve case it is imperative to examine the cerebro-spinal fluid, and to determine the blood Wassermann reaction.

No neurologist would feel confident in diagnosing disseminate sclerosis, without first eliminating the possibility of syphilitic disease. Progressive muscular atrophy may be mimicked by syphilis. Chronic syphilitic meningitis may produce the most diverse clinical syndromes; it may give signs indistinguishable from those of a tumour of the spinal cord, or cause almost any of the lower motor neurone palsies. It is perhaps fortunate that chronic meningitis is present in a large proportion of cases of neurosyphilis, for the changes in the cerebro-spinal fluid which we can detect are largely, if not entirely, due to this. In syphilitic cerebral vascular disease, the cerebro-spinal fluid may be apparently normal, in the absence of syphilitic meningitis.

SYPHILITIC MENINGITIS

The commonest form of this condition is a subacute or chronic inflammation of the pia-arachnoid; it is generally localized at the base of the brain, but may affect any part of the cerebral or spinal meninges. The affected pia is thickened and opaque, from a mononuclear infiltration, and minute gummata may be found along the course of the small vessels. The activity of the process varies in different cases, and with it the degree of change in the cerebro-spinal fluid. Gummata in the substance of the brain, cord, or nerve roots, may be associated with this meningitis. The cerebro-spinal fluid changes depend on the degree of meningeal inflammation. The following changes are commonly found:

The Wassermann reaction of the fluid is positive in 70 to 90 per cent. of cases; the more acute forms of the disease yield the larger percentage of positive reactions. The reaction of the blood is positive in 70 to 80 per cent. of cases.

The fluid is clear and colourless, but contains an excess of cells, practically all of which are lymphocytes. The number of cells varies considerably, being the greater the more active the disease; 10 to 20 per c.mm. are average figures in the chronic form.

Protein is slightly increased, figures usually obtained being 0·03 to 0·05 per cent. Globulin tests are positive.

The chlorides are unaltered.

A clot is usually absent, but may form when the protein is very high.

Lange's Colloidal Gold Reaction

Cerebro-spinal fluid in falling dilutions is mixed with a solution of colloidal gold. The colour of this solution is rose-red, and it is not altered by normal cerebro-spinal fluid in any dilution. In the presence of certain abnormal fluids,

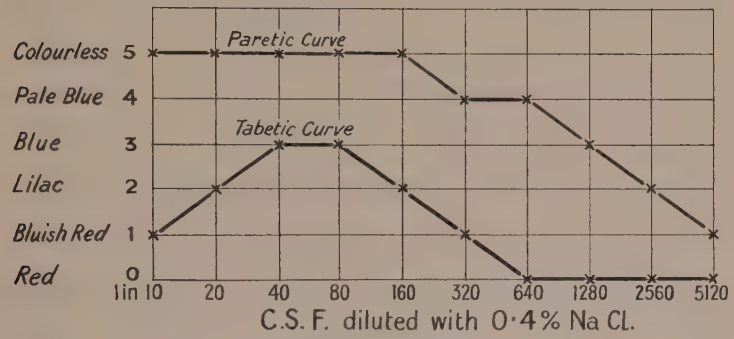

Fig. 1. Lange colloidal gold curves.

varying degrees of precipitation of the gold occur, with alterations in the colour of the mixture. The nature of the test can best be appreciated by referring to the chart, which shows a 'paretic curve' and a 'tabetic curve'. The colour changes are read after standing at room temperature overnight.

The result of a Lange test may be reported in the form of a curve, or in the form of ten figures which indicate the degree of precipitation in the successive dilutions of cerebro-spinal fluid. Thus the paretic curve in the diagram might be reported 5555544321, and the tabetic curve 1233210000.

The reaction is positive in syphilitic meningitis, being usually of the tabetic type. The paretic curve is found not only in G.P.I., but also in tabo-paresis, very occasionally in acute syphilitic meningitis, and in disseminate sclerosis.

A positive Lange is found in conditions other than syphilis of the central nervous system, and is not therefore a pathognomonic sign. The paretic curve is an important diagnostic sign, but any other form of reaction is not of much help.

In a localized spinal meningitis, the fluid in the lumbar region of the theca may be shut off from that above, a condition which gives rise to

The Loculation Syndrome, or Syndrome of Froin

The fluid below such a block differs from that above, in that the protein is greatly increased, and usually the colour yellowish. This may be the result of exudation of serum from the spinal veins, which are running longitudinally, and become distended below the block. The protein is 0·5 per cent. or more; often it is over 1 per cent. The yellowish colour is not invariable. The cells are not increased, except in syphilitic cases.

Froin's syndrome is pathognomonic of spinal compression from any cause.

SYPHILITIC CEREBRAL VASCULAR DISEASE

Produces very slight changes in the cerebro-spinal fluid, unless accompanied by syphilitic meningitis. The fluid may therefore in some cases be normal; but more often, changes such as a slight increase of lymphocytes, and of protein and globulin, indicative of a chronic meningitis, are found. The Wassermann reaction is often negative in the fluid while positive in the blood.

CONGENITAL SYPHILIS

Though many children with congenital syphilis have abnormal cerebro-spinal fluids, even in the absence of nervous symptoms, no diagnostic significance attaches to a normal fluid. Changes such as those described under chronic syphilitic meningitis will be found in many instances.

TABES

The Wassermann reaction is positive in the cerebro-spinal fluid and the blood in about 70 per cent. of cases. A positive Lange reaction, of the tabetic type, will be found in about 60 per cent. of cases.

There is a slight lymphocytosis, weakly positive globulin reactions, and usually normal protein content.

GENERAL PARALYSIS OF THE INSANE

The persistence of the cerebro-spinal fluid changes, in spite of thorough anti-syphilitic treatment, is almost pathognomonic of G.P.I.

The Wassermann reaction is positive in the fluid and blood in almost all cases; if a quantitative test is done, the strength of the reaction in the fluid will show very little alteration after many months of treatment.

A positive Lange reaction of the paretic type is also obtained in all cases, and is equally persistent.

Other changes which will be found are as follows:

Cells increased, from 10 to 500 per c.mm., mainly lymphocytes.

Protein increased, from 0·04 to 0·1 per cent.

Globulin tests positive.

Clot, occasionally.

CHAPTER IV

INFECTIONS OF THE SKIN, VULVA, AND CONJUNCTIVA

STAPHYLOCOCCAL INFECTIONS OF THE SKIN

The staphylococci responsible for skin lesions are *Staphylococcus pyogenes albus* and *Staphylococcus pyogenes aureus*. They are distinguishable from the constant saprophyte of the skin, *Staphylococcus epidermidis albus*, by the fact that they ferment mannite. This white skin staphylococcus is occasionally pathogenic, but its isolation from a skin lesion should always suggest the possibility that its presence may be merely accidental.

The clinical features of these infections are usually unmistakable, and the only reason for isolating the organism concerned is that an autogenous vaccine may be prepared.

Staphylococcus pyogenes albus is not uncommonly responsible for that infection of the hair follicles of the beard known as **Sycosis barbae**, and for the pustules of **Acne**. In furuncles and carbuncles the organism is almost always *Staphylococcus aureus*.

Vaccine Treatment

In the opinion of the majority, the use of vaccines for prophylaxis in those subject to furunculosis is one of the most successful of all applications of vaccine therapy. An autogenous is preferable to a stock vaccine, but this often acts very well. A sensitized vaccine is well worth trial in those people with chronic furunculosis who are peculiarly hypersensitive to an ordinary vaccine.

Careful regulation of the dosage is highly important. A 'reaction', which takes the form of a fresh crop of boils appearing within about twenty-four hours of the injection, should be avoided if possible. To this end the initial dose must be a low one. We have seen unpleasant reactions produced by an initial dose of 100 million organisms, and it should be remembered that one pathologist's 100 millions may differ

very greatly from the 100 millions of another, if different methods of enumeration are used. It is convenient to have two rubber-capped bottles of the vaccine, one containing 100 million organisms per cubic centimetre, the other 1,000 million per cubic centimetre. The following doses given at weekly intervals are suggested as a guide: 25, 25, 50, 50, 100, 100, 200, 300, 400, 500, and so on up to 1,000 millions.

The dosage is the same in the treatment of carbuncles; and when combined with local treatment, results are usually good.

In the pustules of **Acne** the acne bacillus is constantly found associated with the staphylococcus. It is a short, irregular, non-motile Gram-positive bacillus, cultivable with difficulty, best growth being obtained under partially anaerobic conditions.

Although the role of the acne bacillus is still the subject of dispute, the view of Sabouraud that it is the cause of the comedo, while the staphylococcus is responsible for the suppuration, is generally accepted.

Widely differing opinions have been expressed as to the value of vaccine treatment in acne. As a supplement to other methods of treatment it is probably worth trial. A mixed vaccine should be used, containing both the acne bacillus and staphylococcus; a stock vaccine is generally considered to be as efficient as an autogenous one. Injections should be continued for at least six months.

Vaccines are certainly useful in the treatment of **Sycosis barbae**, though results are not comparable to those obtained in furunculosis. An autogenous vaccine should be used, if practicable.

Both acne and sycosis barbae are difficult diseases to cure, and response to vaccines may be very disappointing. Specific therapy takes a secondary place compared with local treatment.

STREPTOCOCCAL INFECTIONS OF THE SKIN

Several skin disorders are the result of infection by *Streptococcus pyogenes*. The diversity of the lesions is

explained partly by the varying depth to which the streptococcus penetrates.

Impetigo contagiosa, for instance, is the result of infection of the most superficial layers of the epidermis. Erysipelas results when the corium is infected, though perhaps the streptococcus concerned here has an unusual degree of virulence. A streptococcal cellulitis follows when infection passes through the skin to the subcutaneous tissues.

These infections, like staphylococcal infections of the skin, are usually recognizable clinically.

IMPETIGO

Pathological Findings

A culture of the serum obtained from vesicles, and from the excoriated surface beneath the crusts, shows the predominating organism to be a streptococcus, usually a *Streptococcus pyogenes*. *Staphylococcus pyogenes* may also be found; the streptococcus is regarded as the primary infective agent.

Treatment

Most cases yield readily to local measures. In some refractory cases a mixed streptococcal and staphylococcal vaccine, preferably autogenous, is a rational measure and has been found of value.

ERYSIPELAS

Pathological Findings

In most cases of erysipelas streptococci do not pass the barriers of the lymph glands draining the infected area. In a small percentage of cases, particularly in children, septicaemia follows. Nephritis also is liable to occur.

The Blood. The most important change is a polymorphonuclear leucocytosis, the total white count being, in the majority of cases, between 10,000 and 30,000 per cubic millimetre.

The Urine. No abnormality is found as a rule, but in severe cases albumin and casts may be present.

The Rash. Near the spreading margin of the red, slightly raised area of infected skin, small vesicles may be found. By means of a fine capillary glass tube it is easy to obtain the fluid contents for film and culture purposes. The *Streptococcus pyogenes* will be found in all cases. The procedure is useful both for diagnosis and treatment.

Treatment

Though specific therapy is generally considered to have little influence on the course of the disease, it is probably wise to use it, in addition to local and general measures; for even in the milder cases serious complications may occur. An intravenous injection of anti-*Streptococcus pyogenes* serum is given, and this is followed by subcutaneous injections of a vaccine, either autogenous, when doses of one to five millions are given on alternate days, or a stock sensitized *Streptococcus pyogenes* vaccine, when much larger doses (e.g. 50 millions increasing to 500 millions or more) can be given at daily intervals.

STREPTOCOCCAL CELLULITIS

The pathological findings differ in no way from those in erysipelas. Specific therapy should here also be given a trial, but is of course quite subsidiary to surgical measures.

MALIGNANT PUSTULE

Infection of the skin with *B. anthracis* is liable to occur in those whose work brings them in contact with the hides of animals. Infection is always traceable to an infected animal, and though cases have been reported where infected shaving brushes were proved responsible, the disease is most likely to be found in butchers, workers in tanneries, and so on.

The lesion is at first like a small furuncle, the central part of which rapidly becomes gangrenous. Much oedema develops around this initial lesion, and the skin becomes red, hard, and brawny. Often a ring of vesicles develops around the central slough. General infection may follow rapidly and lead to death within five or six days.

A lesion of this type, in one whose occupation renders

him liable to infection, demands a bacteriological examination. The diagnosis is made by finding the anthrax bacillus in the vesicles. This investigation is only feasible in a properly equipped laboratory; the practitioner should therefore send any case in which there is a reasonable probability of anthrax infection to the nearest laboratory, with as little delay as possible. A question of hours may decide the outcome.

Three methods are used in examining material from the lesion:

1. Film preparations stained by Gram's method.
2. Cultures on agar; or gelatin stabs.
3. Inoculation of a guinea-pig or a mouse subcutaneously. The animal dies in about forty-eight hours, and the organism is obtained with ease from the blood and organs.

   An opinion must be formed before the result of the animal test can be known, for prompt treatment is essential.

The treatment most generally adopted is excision, combined with the use of an anti-anthrax serum, which should be injected subcutaneously, or intravenously, and into the subcutaneous tissues around the lesion.

RINGWORM

Although the appearance of ringworm is often sufficiently characteristic for diagnosis, in every case an attempt should be made to demonstrate the ringworm fungus in the lesion. Some forms are liable to confusion with other skin diseases, and proof of their nature can only be obtained in this way. For instance, ringworm of the skin may occur, not only in the typical ringed form, but as pinkish, scaly macules liable to confusion with seborrhoeic dermatitis or psoriasis; while the typical greyish, scaly patches covered with opaque hair stumps, which characterize ringworm of the scalp in children, are sometimes masked by secondary infection.

The procedure is extremely simple. In the cases of

ringworm of the skin, moisten the surface of the lesion at the growing edge with liquor potassae (5 per cent. KOH), and scrape it with a scalpel. Transfer scrapings to a drop of liquor potassae on a slide, and examine under a cover-slip; mycelial threads should be visible if the ringworm fungus is present in the lesion. In the case of ringworm of the scalp, or of the beard, pluck out with forceps a suspected hair, place it in a drop of liquor potassae on a slide, and apply a cover-slip. After half an hour the specimen should be clear, and the fungus become easily demonstrable on microscopical examination. Clearing is much quicker if the specimen is heated just short of boiling.

The great majority of ringworms of the scalp in children, and the majority of skin ringworms, are caused by the *Microsporon audouini*. Hardly ever is this a cause of ringworm of the adult scalp; infection of a child's scalp dies out at about puberty. Scrapings from a skin lesion prepared by the method just described show delicate filaments, about 4 μ wide, broken by septa. An infected hair is found to be ensheathed by large numbers of small spores, while filaments may be made out within the hair, lying in its long axis.

Ringworm of the scalp in adults, and some cases of skin ringworm, are caused by a fungus to which is given the generic name of trichophyton. It is characterized by the fact that its spores occur in long chains. In *Trichophyton endothrix* infection, for example, chains of spores are found lying entirely within the hair, in its long axis; while the same arrangement is found in *Trichophyton ecto-endothrix* infection, the cause of suppurative ringworm of the adult scalp, though the fungus in this case is not confined to the interior of the hair.

RINGWORM OF THE NAILS

In this condition, the fungus, a trichophyton, is demonstrable as a rule without difficulty; the diagnosis rests on this finding. A thin shaving of the diseased nail is soaked in hot liquor potassae for an hour or more, mounted on a slide in the same liquid, and examined.

SCABIES

The typical lesions of scabies are often complicated by secondary infection, at times so much so that certain diagnosis is only possible by a demonstration of the *Acarus scabiei*. This is a very simple procedure in most cases, and as it makes diagnosis certain, is of considerable practical value.

A fine needle is inserted into the open end of a burrow (the closed end where the acarus is lying is often marked by a tiny vesicle); the roof of the burrow is gently torn through as the point is directed along to the closed end. When this is reached, the walls of the little cul-de-sac are gently scratched with the point of the needle, and when this is removed, the acarus, just visible to the naked eye, will usually be found clinging to the point.

It is transferred to a slide and examined with the low power of the microscope.

ACTINOMYCOSIS

The skin may be infected with the *Streptothrix actinomyces*, the most common site being the skin of the face and neck. The organism may enter through an abrasion, or the skin may be infected secondarily to the jaw-bones. Several chronic abscesses may develop in a base of hard, brawny, infiltrated skin, the inflammatory process spreading into the subcutaneous and deeper tissues.

The pus is characteristic; it contains large numbers of 'sulphur granules'—yellowish particles about the size of the head of an ordinary pin—which on microscopic examination are readily recognizable as colonies of the streptothrix. Diagnosis is thus easy when nodules have broken down and pus is obtainable.

Treatment

Vaccine therapy is thought to be of value, as an adjunct to the usual methods. It is certainly well worth trial, though we have not observed any good effect following its use in actinomycosis of the internal organs, and the administration of potassium iodide in large doses, together sometimes with surgical measures, will cure most cases of actinomycosis of the skin.

THE SKIN LESIONS OF SYPHILIS

In many cases the examination of a suspicious lesion on the external genitalia for the spirochaete of syphilis will give a diagnosis before it could be obtained in any other way; before, that is, the lesion has become a characteristic chancre, and before the Wassermann reaction is positive. A negative result is inconclusive, but a positive finding is as pathognomonic as laboratory information can be. In all cases when diagnosis is not easy from the clinical features of the case, this method is available and should be used. Extra-genital chancres are often difficult to recognize from their appearance, and in these cases search for the spirochaete is of particular value. Further, syphilitic lesions of the skin may closely imitate a large variety of other skin lesions, and the search for the spirochaete may help in their differentiation.

This examination should be made before treatment has been started, as the spirochaetes rapidly lose their characteristic appearance after injection of the salvarsan group of drugs and for a time after local applications.

We cannot advise the practitioner to attempt the investigation himself; for, although there is no unusual technical difficulty, reliable observation is scarcely possible without a considerable experience of spirochaetes. To obtain serum from the lesion and send it in a sealed tube to a laboratory is of doubtful value; the patient himself should be sent to the pathologist.

Material obtained from the lesion will be examined either by dark-ground illumination, or by one of the silver staining methods. The Indian-ink method is bad for diagnostic purposes, as the organisms are liable to be distorted.

INFECTIONS OF THE VULVA

GONORRHOEAL VULVITIS

The importance of exact bacteriological diagnosis is sufficiently obvious, especially in children, where a simple vulvitis due to other pyogenic organisms is not uncommon. The responsible organism may be demonstrated in film

preparations from the muco-purulent secretion of the inflamed parts. A condition similar clinically to gonococcal vulvitis has been observed, caused by the organisms of Vincent's angina. These were demonstrable in large numbers in the film.

SOFT SORE

This irregular ulcer is liable to be confused with a syphilitic lesion. It is caused by Ducrey's streptobacillus, which is demonstrable without difficulty in film preparations of pus from the ulcer. It should be remembered, however, that mixed infection with the spirochaete of syphilis and Ducrey's bacillus may occur. In such cases the probability is that only Ducrey's bacillus will be found.

SYPHILITIC CONDYLOMATA

The vulva is a common site for these lesions, whose true nature may be diagnosed with certainty by the demonstration of the spirochaete.

DIPHTHERITIC VULVITIS

Primary diphtheritic infection has been met with on the vulva in young children. The diagnosis is confirmed by the usual cultural method. Antitoxin administration is called for, as in faucial diphtheria. Diphtheria of the skin is a very uncommon condition; the cases recorded have mostly been secondary to infections of wounds.

INFECTIONS OF THE CONJUNCTIVA

In any case of conjunctivitis with muco-purulent or purulent discharge, it is wise to determine the nature of the infecting organism. The treatment of the case may be materially affected by this knowledge, as for instance in gonococcal or diphtheritic conjunctivitis. In most cases it can be determined very quickly by a smear of the discharge stained by Gram's method. It is not possible to draw conclusions with any certainty as to the nature of the infection from the clinical features of the case.

ACUTE MUCO-PURULENT CONJUNCTIVITIS

Numerous pathogenic organisms may be responsible for **Acute muco-purulent conjunctivitis**, an affection characterized by a thin muco-purulent secretion which gums the lids together after sleep. Those most commonly found are the Koch-Weeks bacillus, the pneumococcus, streptococci, and staphylococci, and Pfeiffer's bacillus.

When considering bacteriological findings, one should remember that *Staphylococcus albus* is very commonly found in the normal conjunctival sac, as also is the *B. xerosis*, a non-pathogenic diphtheroid. Pneumococci, streptococci, *M. catarrhalis*, and pathogenic staphylococci have also been found in the absence of any inflammatory condition.

It is important to recognize conjunctivitis caused by the Morax-Axenfeld diplobacillus, for there is a method of treating this infection which is wellnigh specific—namely, bathing the conjunctiva with a solution of zinc sulphate. The organism is usually demonstrable without difficulty in a film of the scanty mucoid exudate, stained by Gram's method. It is a Gram-negative diplobacillus, in length two to three times the diameter of a staphylococcus.

Purulent conjunctivitis in the new-born—'ophthalmia neonatorum'—is most commonly a gonococcal infection; pneumococcal and streptococcal cases are sometimes met with. In adults purulent conjunctivitis is usually gonococcal, but other organisms may be responsible. Streptococci, pneumococci, the Koch-Weeks bacillus, the Klebs-Loeffler bacillus, may all give rise to this condition. In the gonococcal cases infection is almost always due to direct transference of discharge from the genitals to the eyes; in the presence of a urethral discharge, therefore, the probability that a purulent conjunctivitis is gonococcal is very strong. But it is wise in all cases to make the bacteriological diagnosis by examination of a film of the conjunctival pus.

Cases of acute conjunctivitis in which a fibrinous membrane forms on the surface of the conjunctiva are not common. This **membranous conjunctivitis** is very suggestive

of infection by the diphtheria bacillus, but a membrane is not conclusive evidence. In such a case bacteriological investigation is highly important; a swab, or the patient, should be sent to a bacteriological laboratory. A little of the exudate is obtained with a platinum loop or a tiny wool swab, smeared over a serum slope, and two films made, exactly as in the examination of the fauces when faucial diphtheria is suspected.

Two facts are to be kept in mind in making this examination: first, there may be secondary invaders, such as streptococci or pneumococci : the presence of these in the film does not exclude the diphtheria bacillus. Secondly, a diphtheroid bacillus is present in the normal conjunctival sac; great care must be taken that this organism and the diphtheria bacillus are not confused. Morphologically, they are identical, or the difference is so slight that they cannot be distinguished from their appearance; neither is differentiation possible by cultural characters. *B. xerosis* ferments saccharose, *B. diphtheriae* does not; but the most important distinction is that *B. xerosis* is a harmless saprophyte, it produces no toxin, and a broth culture injected into a guinea-pig is without effect, whereas a guinea-pig injected subcutaneously with a broth culture of *B. diphtheriae* dies within a few days. This is the only reliable test, but it takes so long that all cases of membranous conjunctivitis should be treated as diphtheritic, by injection of antitoxin and application of the serum to the conjunctiva, until this possibility has been excluded.

CHAPTER V

INFECTIONS OF THE MOUTH, NOSE, AND THROAT

1. NASAL AND POST-NASAL CATARRH

General Considerations

This condition is one of the most troublesome of all minor maladies, both to the patient and to the doctor. An acute rhinitis is usually a prominent feature of the '*common cold*'—an acute catarrh of the upper air passages which lasts about one week, and which is often followed by a chronic catarrh of indefinite duration, with much mucopurulent secretion. The inflammation may spread to the nasal sinuses or to the middle ear in patients whose resistance is unusually low, or where the infective agent is of unusual virulence.

An acute catarrh attacking healthy nasal and nasopharyngeal mucous membranes is perhaps the commonest form of 'cold in the head', but there are many patients in whom the pathology is a little different. These have constantly a chronic nasal or post-nasal catarrh. At no period is the nose free from excessive mucous discharge, which may be more or less purulent, and at intervals the infection flares up with the usual symptoms of acute rhinitis.

It is most important to recognize a *sinusitis*. An acute infection of the sinuses may have serious sequelae if it is not efficiently treated, while a chronic sinusitis is responsible for many cases of persistent chronic nasal discharge resisting all efforts at treatment unless the underlying sinus infection is adequately dealt with. Acute sinusitis during the course of an acute nasal catarrh is suggested by pain and tenderness in the region of the sinus, and acute suppuration may be accompanied by severe general symptoms. In all cases of chronic nasal or post-nasal catarrh and obstruction which resist the usual local treatment, a chronic sinus infection should be suspected, especially if accompanied by neuralgic pains in the head.

Chronic rhinitis is a generic term applied to several different

conditions of the nose. The form of chronic catarrh known as 'chronic hypertrophic rhinitis' is commonly associated with recurrent attacks of acute rhinitis. In some cases it may be the result of these attacks; while in others it is the underlying condition. In children it is commonly an expression of chronically infected adenoids; in other patients chronic sinus suppuration, or a deformed nasal septum, is responsible for the persistence of such chronic catarrh. Nasal obstruction and greatly increased secretion of mucus are the prominent symptoms.

Chronic Atrophic rhinitis has no connexion with this condition. Its aetiology is quite unknown, but it seems probable, from the intensely offensive and characteristic odour which often accompanies it, that it is a chronic infection by some putrefactive organism. *Bacillus foetidus ozaenae* of Perez has been found associated with this condition.

Pathological Findings

Acute Rhinitis

A single bacteriological examination of the naso-pharynx during the course of a 'common cold' reveals a very varied flora in most instances; bearing in mind the fact that there is a 'normal flora' of the upper air passages, we can rarely feel sure, in uncomplicated cases, that we have isolated pathogenic organisms.

The bacteriology of this condition has not been studied very extensively. In the nasal cavities themselves there is no normal flora, for the nasal mucous membrane is inimical to the growth of organisms; and, moreover, organisms inhaled are constantly swept back to the pharynx by the ciliated epithelium.

In the anterior part of the nasal cavities a great variety of organisms may be met with, including diphtheroid bacilli, pneumococci, staphylococci, streptococci, and many non-pathogenic species.

The following are some of the conclusions arrived at by Bloomfield in a careful investigation of the bacteriology of the throat in a series of cases (29).

The organisms in the normal throat may be divided into

1. Members of the constant normal flora—
   Gram-negative cocci and non-haemolytic streptococci.
2. Organisms found in a large number of healthy throats and which may be present over a considerable period of time—
   pneumococci and Gram-negative haemophilic bacilli (the Pfeiffer group).
3. A group of organisms commonly present about the body, but which when introduced into the mouth have only a transient existence there—
   staphylococci and other large Gram-positive cocci, diphtheroid bacilli, and haemolytic streptococci. These organisms disappear in a few days as a rule, as happens experimentally when foreign organisms are introduced into the mouth. Members of this group only occur in the throat over long periods of time when there is some local disease.

In cases of acute coryza free from complications, such as sinusitis, laryngitis, and bronchitis, the flora differs from that of the healthy upper air passages in no essential way. Non-haemolytic streptococci and Gram-negative cocci are constantly present, and there is also a transient flora of various organisms as in normal individuals. From various considerations it would seem that the most probable cause of ordinary uncomplicated acute coryza is a filtrable virus. Thus Kruse collected secretion from the nose of a patient with an acute cold, diluted it with saline, filtered this through a Berkefeld filter, and instilled the filtrate into the nasal passages of thirty-six healthy people; fifteen developed typical colds after two or three days. This experiment has been repeated and the result confirmed.

Cases with a complication show quite different features; in them it is easy to determine the organism responsible for the complication. Thus in Bloomfield's series, coincidently with the development of tonsillitis during the course of a 'cold', innumerable colonies of a haemolytic streptococcus were obtained, which disappeared as the

tonsillitis subsided. In another case bronchitis was associated with a pneumococcus in pure culture from the bronchial pus.

It is important to distinguish those cases of acute coryza which are exacerbations of a chronic infection. This is quite a common type of recurrent 'cold', and in these repeated attacks it is common to find the same organism, often in almost pure culture; an organism which is also found, though perhaps in smaller numbers, during the chronic stage.

In view of our imperfect knowledge of the bacteriology of these infections, and of the different clinical conditions to which the label 'common cold' is often applied, it is small wonder that vaccine treatment and prophylaxis give such inconstant results. Before undertaking bacteriological investigation for this purpose the most careful attention should be given to the clinical type to which the case belongs. Summarizing the above remarks, the case may be:

1. An ordinary uncomplicated 'cold', arising in a previously healthy naso-pharynx. The cause of this type is probably a filtrable virus. Bacteria present are identical with those in the normal upper air passages, though perhaps growing in greater profusion, and have no causal association with the condition. Many are transient, as successive cultures will show.

2. The above type in which some complication such as tonsillitis, laryngitis, or sinusitis has developed. These complications are due to pathogenic organisms such as staphylococci, pneumococci, and streptococci. The identification of the organism concerned is not difficult.

3. An exacerbation of a chronic catarrh. The cause of acute rhinitis of this type may be bacterial; it often largely predominates in cultures, and is present constantly both in the acute and chronic stage.

4. Present knowledge is too imperfect to enable one to say that the above are the only possible types of acute coryza. It may be that some pathogenic bacteria gaining access to healthy nasal cavities may cause an ordinary uncomplicated catarrh. Experimental instillation into the

nose of a culture of *B. coryzae segmentosus* has produced such an attack. Nevertheless, it cannot be too strongly emphasized that interpretation of the results of bacteriological examination during an ordinary attack of acute coryza is difficult. In the majority of cases no one of the organisms isolated is the cause of the condition.

Chronic Rhinitis

It is most important to remember that chronic hypertrophic rhinitis may be a symptom of some local condition, such as chronically infected adenoids or chronic sinusitis. The organisms responsible for these primary infections may be found in the nasal discharge.

Specific Therapy

The results obtained by vaccine therapy will depend largely on the care with which cases are selected for treatment. It is courting failure to expect to cure chronic rhinitis by a vaccine if a deformed septum causes retention of the secretion or if there is an underlying sinus infection.

Prophylactic treatment by vaccines of an acute coryza which arises in a healthy mucous membrane—either autogenous, prepared from the secondary invaders in the later stages, or stock, composed of similar organisms—can do little more than prevent to some extent the subacute catarrh which follows the acute invasion, so shortening the whole attack. But this is well worth attempting, especially during a severe epidemic of colds.

In that type of recurrent cold which arises on the basis of a chronic catarrh, an autogenous vaccine should be prepared, after bacteriological examination both in the acute and chronic stages. With proper use of such a vaccine, good results may be expected with some confidence. The nature of the organisms responsible will influence the results to some extent. Harmer (30) found that in this class of case the commonest infections were (1) Pfeiffer's bacillus and the pneumococcus, and (2) the pneumococcus and *M. catarrhalis*; in his series better results were obtained in the second group. The first dose of the vaccine should be a small

one; it should not be larger than one to five millions in the case of Pfeiffer's bacillus and the pneumococcus, or five to ten millions for *M. catarrhalis.* It will be found that some patients are very sensitive, and may show quite severe reactions if larger doses are used at the outset. No rule can be given for the duration of treatment. If little improvement is observable after six to eight weeks, it is wise to have the secretion examined again; some new organism may appear in the cultures and the vaccine need modification.

In purulent rhinitis—which is thought to be the early stage of chronic atrophic rhinitis—vaccine therapy may well be employed in addition to other measures; many cases are markedly benefited.

Chronic sinusitis is very rarely improved by vaccine treatment.

Material for examination may be obtained by instructing the patient to blow his nose into the middle of a clean handkerchief. The handkerchief is then refolded, enclosed in a tin, and sent to the pathologist. A clean handkerchief, before it is unfolded, is sufficiently sterile for the purpose.

If the catarrh is mainly post-nasal, it is better to take a specimen of post-nasal secretion by means of a swab, or to send the patient to the clinical pathologist for this purpose.

2. DIPHTHERIA

General Considerations

Diphtheria is a local inflammation by the Klebs-Loeffler bacillus, with severe general symptoms from absorption of the exotoxin produced by the organism. The commonest site of infection is the fauces; naso-pharynx, nose, larynx, and trachea follow in order of frequency. In the great majority of cases the diphtheria bacillus remains at the site of local infection, though in a very small number of cases it has been found in the blood-stream during life. The local lesion results in the formation of a characteristic membrane; the bacillus first destroys the superficial cells of the mucous membrane, and this injury is followed by a coagulable exudate. The membrane consists of fibrin entangling dead

epithelial cells, blood-cells, and large numbers of bacilli. Secondary invasion of the affected area by streptococci and other pathogenic organisms is not uncommon, and a secondary broncho-pneumonia due to these organisms is not an infrequent complication of faucial diphtheria.

Difficulties in diagnosis on clinical grounds alone are not infrequent, and the value of bacteriological examination in suspected cases can hardly be over-estimated. The mild forms of faucial diphtheria may be no more than a catarrhal inflammation without typical membrane. No membrane may be visible in laryngeal diphtheria in children, and when there is the least doubt that the case is not one of simple catarrhal laryngitis it must be treated as one of diphtheria pending the result of bacteriological examination. Nasal diphtheria usually manifests itself as a chronic rhinitis without constitutional symptoms; but such cases are a source of infection. Naso-pharyngeal diphtheria has the same general symptoms as the more common faucial type.

Virulent diphtheria bacilli often remain in the throat for several weeks of convalescence, and some cases become chronic carriers of the organism. Outbreaks of diphtheria are commonly traceable to 'carriers'. An investigation aims chiefly at their detection. When cases of diphtheria occur in a school, for example, all possible contacts are examined, and those showing unhealthy conditions of the nose and throat submitted to bacteriological examination. In this way it is often possible to detect a carrier, and by taking suitable measures to control the spread of infection.

Laboratory Diagnosis of Diphtheria

Strictly speaking, this of course is not possible. In only one or two diseases can a diagnosis be made with certainty on the result of a laboratory investigation only. The bacteriologist finds the Klebs-Loeffler bacillus or he does not find it. The positive result very greatly strengthens clinical evidence of diphtheria, but is not diagnostic in the absence of such evidence. The negative result will not upset a diagnosis which has been made with confidence upon purely clinical grounds. It may be well to emphasize

at this point that in all cases where the clinical features are suggestive of diphtheria, antitoxic serum should be administered without waiting for the bacteriologist's report. The examination of a swab is of most help in those cases where the diagnosis is doubtful; although in such cases the finding of the Klebs-Loeffler bacillus is not in the nature of a crucial instance, the evidence should be regarded as sufficiently strong to warrant the administration of antitoxin.

The physician will usually send material for examination from cases of clinical faucial diphtheria. In such cases a bacteriological diagnosis can be made with confidence in twenty-four hours by the examination of stained films from cultures of the swab. Although the bacillus cannot be identified with certainty on morphological characters alone, there is a very high degree of probability that an organism morphologically resembling the Klebs-Loeffler bacillus **when obtained from inflamed fauces** is actually the diphtheria bacillus; for non-virulent strains have been found very rarely from this source.

In all other cases submitted to bacteriological investigation—in suspected nasal diphtheria, for example, and in the case of throats examined for the detection of diphtheria carriers—the diphtheria bacillus cannot be identified without having recourse to a virulence test and a study of the sugar reactions of the organism.

The bacteriologist should always carry out these confirmatory tests in such cases, for it is not uncommon to isolate closely allied organisms which are avirulent and are not to be regarded as diphtheria bacilli, although their morphological characters are identical.

The best material to send for examination is of course a portion of membrane: in practice the usual throat swab is rubbed over a patch of membrane, if such is present, and sent to the bacteriologist with the minimum delay—though there is little risk of the organism's dying during transmission through the post. The bacillus, while present in very large numbers in the membrane, is also to be found in the surrounding parts of the fauces and in the mouth.

In cases where no membrane is present, as in suspected laryngeal diphtheria in children, the wool swab is swept over the tonsils and pillars of the fauces. In suspected nasal diphtheria the turbinal bones are swabbed through the anterior nares; in these cases, and for the detection of diphtheria carriers, it is essential to send the swab to a laboratory where facilities exist for animal experiments. It should be remembered that a smear as well as a culture should be examined as a routine; for Vincent's angina not infrequently may simulate diphtheria. In that condition the diagnosis can only be made from the smear, for the organism cannot be cultivated on ordinary media.

The Serum Treatment of Diphtheria

It is perhaps still important to emphasize the urgency of serum administration in all suspected cases of diphtheria. Only in those cases where the diagnosis is very doubtful is it permissible to wait for the bacteriologist's report. From figures given in the Medical Research Council's monograph on diphtheria, it would appear that the danger of toxic symptoms arising from sensitivity to horse serum has been greatly exaggerated. Serum sickness, characterized usually by urticaria and painful joints, is very common, occurring in well over fifty per cent. of cases, according to the amount of serum injected; but serious symptoms of collapse, even after a second injection of serum, are extremely rare. A study of the information on this subject given in the monograph referred to is quite convincing that the possibility of these accidents should never deter a physician from giving antitoxic serum in suspected cases of diphtheria. It is even doubtful whether the anaphylactic shock which may be produced experimentally in animals ever occurs in human beings.

The best method of administration of the serum in cases of ordinary severity is by intramuscular injection. By this route there is a maximum amount of antitoxin in the blood in twenty-four hours, whereas this is not so for as long as three days when the serum is injected subcutaneously. Intravenous injection should be adopted in severe

cases; serum sickness is rather more frequent and more severe after intravenous injection, and the first few cubic centimetres should be injected very slowly, especially if the patient has received a previous injection of horse serum. No further attempt at 'desensitization' need be made.

Dosage should be based on the following table (quoted in the Medical Research Council's monograph). Modern teaching is that one injection only should be made, consisting of the total quantity of serum which is thought necessary.

(Park 1921)

	Mild cases	*Early moderate*	*Late moderate and early severe*	*Severe and malignant*
Infants 10–30 lb. in weight: under two years.	2,000–3,000	3,000–5,000	5,000–10,000	7,500–10,000
Children 30–90 lb. in weight: under fifteen years.	3,000–4,000	4,000–10,000	10,000–15,000	10,000–20,000
Adults 90 lb. and over in weight.	3,000–5,000	5,000–10,000	10,000–20,000	20,000–50,000
Method of administration advised.	intramuscular	intramuscular	intravenous	intravenous.

THE DIPHTHERIA CARRIER

In the great majority of convalescents diphtheria bacilli disappear from the upper air passages in a comparatively short time; about 60 per cent. are free in three weeks, and over 90 per cent. are free in six to ten weeks; exceptional cases may remain carriers for many months.

The rate of natural disappearance of the organism in healthy carriers is much the same, though it proceeds rather more slowly; and again a few remain chronic carriers.

The presence of any unhealthy conditions of the nose and throat, such as enlarged and infected tonsils and adenoids, predisposes to the chronic carrier state. Such carriers are rapidly cured after removal of the tonsils.

In the treatment of carriers, nothing should be done beyond local antiseptic measures for about ten weeks, when in the majority of cases spontaneous cure will have occurred. If virulent bacilli are still present, removal of tonsils, or operation for any obstructive condition of the nose, if such exist, may be advised. Carriers are immune to diphtheria.

THE SCHICK TEST AND IMMUNIZATION AGAINST DIPHTHERIA

The Schick test consists in the intracutaneous injection of a known small quantity of diphtheria toxin. The amount of toxin used is such that if the patient's serum contains enough antitoxin to confer immunity to the disease, no reaction will follow the skin injection. If, on the other hand, the patient's serum contains no antitoxin or only very small quantities, a red flush develops at the site of injection in twenty-four to thirty-six hours, reaching its maximum in four days.

Thus the test may be used for separating people who are immune to diphtheria from those who are susceptible. As it is probably possible to immunize artificially the majority of susceptible individuals, this information must prove of great value in the prevention of diphtheria, and the test will no doubt become the recognized method of dealing with outbreaks in schools and other institutions. It has already been employed on a large scale in America, and statistics prove its value.

In practice the toxin is injected into the skin of one arm, and an equal quantity of toxin which has been heated to 70° C. for five minutes is injected into the skin of the other arm. This control is necessary because the crude 'toxin' contains other substances which cause in some people 'pseudo' reactions, which would otherwise be misinterpreted. The heating destroys the toxin, but not the substance which may give a 'pseudo' reaction.

0·2 c.cm., containing 1/50th of a minimal lethal dose of diphtheria toxin for a 250 gramme guinea-pig, has to be injected. This is obtained by diluting crude toxin with

sterile saline just before use: the diluted toxin cannot be kept for more than twenty-four hours, while the undiluted material lasts about twelve months. Messrs. Burroughs Wellcome & Co. supply outfits consisting of undiluted toxin, control, and diluting fluid, whereby the requisite dose of toxin is readily prepared. Two 1 c.cm. syringes, with fine needles $\frac{1}{4}$ inch long, are needed, one for the toxin, the other for the control. After cleaning the skin of the forearm with spirit, the needle is introduced *into* the epidermis, parallel to the surface: it should be possible to see the point of the needle through the horny layer of the skin. 0·2 c.cm. is then injected: a small wheal indicates that the injection has been properly made.

Four types of reaction may be observed:

1. Negative.
2. Positive: A red flush appears in from twenty-four to thirty-six hours at the site of injection of the toxin: this is of maximum degree and extent in four days, when some slight swelling appears. Nothing happens where the heated toxin has been injected.
3. Pseudo: A red flush develops within twenty-four hours, *and to the same extent on both arms*. It has practically gone after four days.
4. Positive and pseudo: This is a combination of 2 and 3. If the arm is examined about the fourth day, the reaction on the test arm is at its maximum while that on the control arm is fading.

By the injection of a toxin-antitoxin mixture, it has been possible to immunize a large proportion of children who give a positive Schick reaction, so that after a variable interval the reaction becomes negative. Three doses of 1 c.cm. of the mixture are injected subcutaneously, at weekly or fortnightly intervals. Usually there is no ill effect from these injections in children, except in those who show a positive and pseudo Schick reaction, when local tenderness and swelling with some constitutional disturbance often appear. Statistics given by Park in New York (1922) fully demonstrate the value of this method in reduc-

ing the incidence of diphtheria. Immunity so produced is apparently permanent. Should an attack of diphtheria occur in an immunized individual, an occurrence of considerable rarity, it is mild in character.

3. VINCENT'S ANGINA

This is an ulceration of the fauces, with formation of a membrane, usually met with in debilitated patients. Two organisms, growing in symbiosis, are constantly found in films of swabs taken from the ulcer. These are a fusiform bacillus, and a long spirochaete with coarse irregular coils. Both are readily recognizable in properly stained preparations: the spirochaete stains with difficulty, and the film should be allowed $\frac{1}{4}$ hour in methylene blue—that is, very much longer than is required for most organisms.

The local condition may closely resemble diphtheria, especially in the first day or two. This is one reason why the bacteriologist always examines a direct film from a swab taken for the diagnosis of diphtheria, in addition to making a culture. Cases of Vincent's angina would otherwise be missed, as the spirochaete is not cultivable on ordinary media.

The chief clinical distinctions from diphtheria are these—the condition is usually limited to one tonsil, though it may spread and involve neighbouring tissue; the membrane is soft and friable; constitutional symptoms are mild.

4. SCARLET FEVER

General Considerations

Sore throat occurs with great constancy at the onset of scarlet fever. The appearance is one of a brilliant red injection of the tonsils and fauces. In more severe cases after five or six days, a yellow membrane may form on the tonsils, and may spread to neighbouring parts of the fauces. Such a membrane may easily be confused with that of diphtheria, but microscopical examination will show large numbers of haemolytic streptococci, while the Klebs-Loeffler bacillus is absent; and moreover the membrane is soft and friable in contrast to the tougher and more adherent membrane

of diphtheria. In this connexion it should be remembered that scarlet fever convalescents are peculiarly susceptible to diphtheria, so that a membrane appearing late in the disease may quite well be diphtheritic. It is wise in all cases of membranous angina to have a swab bacteriologically examined.

Cases of more severe faucial inflammation occur, with correspondingly severe general symptoms, in the type described as scarlatina anginosa: there is considerable oedema of the fauces and palate and sometimes of the larynx. Ulceration of the tonsils and fauces may occur and may lead to perforation of the soft palate.

The view most generally accepted at the present time of the nature of scarlet fever is that it consists in an acute inflammation of the tonsils and fauces by a specific streptococcus which gives rise to the production of a soluble exotoxin; absorption of this toxin causes the general symptoms characteristic of the disease.

It has been known for many years that a streptococcus is to be found in abundance in the tonsillar and faucial secretion at the onset of scarlet fever, and that this organism is responsible for the adenitis, rhinitis, or otitis which may complicate the disease. This streptococcus was found by Gordon to be indistinguishable from *Streptococcus pyogenes* in cultural and biochemical characters and as regards virulence for the mouse. In 1920 Tunnicliffe and Bliss showed that this scarlatinal streptococcus has serological characters which are quite distinct from those of *Streptococcus pyogenes*; this was confirmed in 1921 by Gordon's observations. All examples of *Streptococcus scarlatinae* fall into one well-defined serological type. The hypothesis suggested by Klein in 1887, that a streptococcus is the essential cause of scarlet fever, has scarcely been accepted until quite recently. Certain observations, chiefly of American investigators, lend considerable probability to this view. G. F. and G. H. Dick (31) record the case of a nurse taking care of a patient with scarlet fever, who developed a sore finger and two days later typical scarlet fever. Cultures of the pus from her finger yielded a haemolytic

streptococcus and a diphtheroid bacillus. The streptococcus was isolated in pure culture and five volunteers were swabbed over the tonsils and fauces with this organism; one of them developed typical mild scarlet fever. A further five volunteers were swabbed with a filtered culture of the organism; all remained well for ten or twelve days, and were then swabbed with an unfiltered culture. Again one volunteer developed typical scarlet fever.

The same workers in 1924 (32) described the effects of intracutaneous injection of the toxin produced by *Streptococcus scarlatinae*. The Berkefeld filtrate of a culture of a haemolytic streptococcus isolated from a case of scarlet fever was used, being injected in amounts of 0·1 c.cm. of a 1 in 1,000 dilution into the skin of the anterior surface of the forearm. As a control the undiluted sterile culture medium was similarly injected in another area. In certain cases erythema and swelling of the skin appeared at the site of injection of the toxin within four to six hours, attaining a maximum in eighteen to thirty-six hours. Such a positive reaction was obtained in 41·6 per cent. of persons with no history of scarlet fever, whereas all scarlet fever convalescents showed negative or very slightly positive reactions. The effect is inhibited if the serum from a scarlet fever convalescent is mixed with the filtrate before injection. It is inferred that a negative reaction indicates the presence of antitoxin in the serum of the person tested, and that we have in this reaction a test for susceptibility to scarlet fever.

In 1918 Schultz and Charlton (33) showed that an intracutaneous injection of serum from a patient convalescent from scarlet fever produced in patients with scarlet fever, with the rash fully developed, a local area of blanching. It would thus seem very probable that the immunity developing in scarlet fever is antitoxic, and that this 'rash-extinction test' is due to neutralization of a toxin *in situ*.

From these observations, the hypothesis that *Streptococcus scarlatinae* is the essential cause of scarlet fever would seem to be well established, and we shall find further support in the therapeutic effect of an artificially prepared antitoxic serum, to be described immediately.

LABORATORY METHODS IN DIAGNOSIS, TREATMENT, AND PROPHYLAXIS

Diagnosis

The Schultz-Charlton phenomenon (blanching effect; rash-extinction test) may prove a useful diagnostic test. Blake, Trask, and Lynch (34) found that injection of 0·02 c.cm. to 0·5 c.cm. of a serum prepared by immunizing a horse with *Streptococcus scarlatinae* produced an area of blanching at the site of injection in every case of scarlet fever tested. It persisted until the rash had completely faded. At present the effect of this serum on other rashes has not been sufficiently observed.

Treatment

Evidence is accumulating that an artificially prepared antitoxic serum has a very definite therapeutic value. Blake, Trask, and Lynch in 1924 reported that in two mild cases, five moderately severe cases, and three severely toxic cases, a single intramuscular injection of 40 to 60 c.cm. of serum was followed by a prompt and complete recovery within twelve to twenty-four hours. The temperature fell to normal in eight to twelve hours, the rash completely disappeared in twelve to twenty-four hours, and a rapid improvement in the angina took place. In two extremely toxic cases with almost hopeless prognoses injection of larger amounts of serum was followed by recovery in thirty-six hours. One case died, a septic case with streptococcal septicaemia and severe cervical adenitis.

Anderson and Leonard (35) describe their method of preparing antitoxic serum by immunization of horses with filtered cultures of *Streptococcus scarlatinae*, and the results of its therapeutic application. They conclude that this serum is an effective prophylactic if used in adequate doses, namely, not less than half the average therapeutic dose. Intravenous administration in cases of scarlet fever was followed by a fall of temperature to normal within twenty-four hours, a marked diminution of the rash, improvement in the general condition of the patient, and a reduction in complications and sequelae. Antiscarlatinal serum is to be obtained from most reputable firms.

Prophylaxis

Further investigations have tended to confirm the view that the Dick test provides a means of separating persons who are susceptible to scarlet fever from those who are immune. Thus Joe (36), in 1925, records that 95 per cent. of cases of scarlet fever in the first five days of illness give a positive reaction, whereas from the thirty-first to the thirty-fifth day only 4·76 per cent. were found positive. Between these two periods there was a gradual decline in the percentage rate. In patients not suffering from the disease, between the ages of 1 and 5 years, 55 to 60 per cent. gave positive reactions. In persons with a previous history of scarlet fever, over 88 per cent. were found negative.

It seems highly probable that the Dick test has the same value in scarlet fever as the Schick test in diphtheria, and if prophylactic immunization of susceptible persons proves practicable, the control of scarlet fever will be greatly advanced. Scarlet fever toxin for this purpose appears to be of value. It is used in the same way as is the Dick toxin-antitoxin mixture, and can be obtained commercially. The ideal dosage is as yet not fully worked out, but a usual procedure is to give three injections at weekly intervals of 500, 1,500, and 3,000 skin doses. Some authorities advise higher final dosage, up to 30,000, and the second interval should ideally be longer than a week—three or four weeks (37).

CHAPTER VI

FOCAL INFECTIONS AND DISEASES ARISING THEREFROM

General Considerations

The concept of the production of disease by a localized area of infected tissue has received much attention in recent years. It has provoked more acrimony than almost any other pathological hypothesis.

Chronic focal sepsis is a very common condition in otherwise healthy individuals, and it has been assigned a causal relationship with many disorders of obscure aetiology on perhaps insecure grounds. Evidence is now, however, irrefutable that focal sepsis is an essential factor in certain diseases, and that the first step in the treatment of such diseases is to seek out and eradicate this primary infection.

Billings (38) describes foci of infection as primary and secondary. A primary focus is usually in tissue communicating with a mucous membrane; from a primary focus infection may spread, either directly or by the blood or lymph, and a secondary focus may form. This may persist after the primary focus has disappeared.

It will be convenient to omit from this section a consideration of most acute infections arising secondarily to acute primary foci; the causal relation is as a rule sufficiently obvious. Chronic focal sepsis as a factor in disease presents a more difficult problem. In the following account the common primary foci, with the bacteriological findings in each case, are considered first; after this some attention is given to the disorders in the aetiology of which focal sepsis is thought to play an essential part.

THE PRIMARY INFECTIVE FOCI

THE NORMAL FLORA OF THE MOUTH

If successive cultures are made from a healthy mouth, it will be found that there is a constant normal flora consisting of non-haemolytic streptococci and *M. catarrhalis*. Other

organisms may pass a more or less transient existence there. For instance, *Staphylococcus albus* and pneumococci are very frequently found, while *Staphylococcus aureus* and *Streptococcus haemolyticus* may be present in the absence of obvious disease. Other Gram-positive cocci, as *M. tetragenus*, are very common. Diphtheroid bacilli, *Friedlander's bacillus*, and various members of the coliform group may be present from time to time.

In addition to these organisms the direct examination of films of scrapings from the mucous membrane, especially that around the base of a tooth, will often show thread-like organisms, the *B. fusiformis* of Vincent, and numerous spirochaetes. The thread-like organisms include both members of the leptothrix group, simple threads which do not branch, and of the streptothrix group, threads showing true branching. The mouth spirochaetes are of numerous kinds, the following being the better known: *Spironema vincenti*, *Treponema macrodentium* (an organism with a marked resemblance to *Treponema pallidum*), *Treponema microdentium*, and *Leptospira dentium*.

With the exception of Vincent's spirochaete there is no evidence that mouth spirochaetes are ever pathogenic for man.

PERI-APICAL INFECTION

In almost all cases where a radiogram shows rarefaction in the peri-apical region, the root will be found to be infected. In the great majority of such cases organisms have invaded the peri-apical regions from the infected tooth pulp. (For method of culture see p. 372.)

With aerobic technique streptococci are isolated in practically all cases. In the great majority these are members of the streptococcus viridans group. Sometimes they are isolated in pure culture, but more frequently they are mixed with other organisms. Haemolytic streptococci are not common: they are probably found in from 5 to 10 per cent. of cases. Of other organisms, *Staphylococcus aureus*, *Staphylococcus albus*, *M. catarrhalis*, and diphtheroid bacilli are met with fairly commonly. There is a general belief

that the primary infecting organism is the *Streptococcus viridans*.

Anaerobic technique is never employed as a routine, and though it is probable that strict anaerobes are invariably present, we know nothing as to their pathogenicity.

PYORRHOEA ALVEOLARIS

The first change which leads to pyorrhoea alveolaris is an atrophy of the margin of the alveolar process around the teeth, with falling away of the gums from the teeth and formation of pockets. Such pockets readily become infected with micro-organisms, with formation of pus which has a ready access to the surface. Film preparations of the pus show a great variety of organisms. Compared with what we find in peri-apical infections, the number of species encountered is considerably greater, a fact which is readily explained by the easy access of stagnant food particles to the infected sockets.

A vast amount of work has been done to determine the bacteriological cause of pyorrhoea, from which the view has emerged that the condition is a mixed infection from the outset and that there is no specific cause. Two types of organisms are found with great constancy: streptococci, especially those of the non-haemolytic group, and spirochaetes. By some authorities the non-haemolytic streptococci are regarded as the most important causal factor; and by others spirochaetes, which are present in very large numbers in almost all cases, are thought to be primarily responsible. Other organisms very commonly found are *B. fusiformis*, staphylococci, *M. tetragenus*, pneumococci, *M. catarrhalis*, diphtheroid bacilli, and many others.

From the point of view of systemic disease, the constant presence of streptococci may be of importance.

TONSILLITIS

It is not always easy to decide whether the tonsils are infected; in fact decision may sometimes be impossible. The examination of a swab from their surface does not often help, for almost any of the organisms responsible for

a chronic tonsillitis may be present in the mouth in the absence of disease. We have only clinical evidence, and it is to be remembered that chronically inflamed tonsils may be enlarged, atrophied, or normal in size. The condition may be due to, or associated with, a recurring acute tonsillitis. Rehfuss (39), in discussing the relation of focal sepsis in disease of the stomach, quotes observations which have shown that most cases of benefit after removal of tonsils have been in those patients giving a history of repeated attacks of tonsillitis. He condemns the tonsils if the patient has had acute tonsillitis; if a swab shows a pathogenic organism definitely predominating, particularly if this is a haemolytic streptococcus, and of course if examination shows inflamed tissue from which true pus, as distinct from normal crypt secretion or food, can be obtained.

Bacteriological examination of the tonsils in these cases is of most value after their removal. A mixed flora will most likely be obtained, but often non-haemolytic streptococci predominate. Haemolytic streptococci are very common, and pneumococci, *M. catarrhalis*, staphylococci, Pfeiffer's bacillus, diphtheroid bacilli, and others often occur.

SINUSITIS

In the search for a primary focus, patients with persistent nasal discharge, especially if associated with localized pain and severe headache of unexplained origin, should be referred to a nose and throat specialist for examination. The maxillary sinus, the ethmoidal sinuses, and the sphenoidal sinus, as sites of focal sepsis associated with systemic disease, are of most importance. From the mucopurulent secretion of chronic sinusitis a variety of organisms may be obtained: common are, streptococci, both haemolytic and non-haemolytic; pneumococci; *M. catarrhalis*; Pfeiffer's bacillus; staphylococci; Friedlander's bacillus; and occasionally *B. proteus* and other coliform organisms.

CHRONIC CHOLECYSTITIS

Chronic cholecystitis may act as a primary focus, but it may sometimes be itself a metastatic infection associated

with primary foci in the head. It is possible to obtain a sample of bile for bacteriological examination by means of the duodenal tube. Rehfuss recommends that after the duodenal tube has been passed, suction be applied at intervals until the characteristic thick, dark gall-bladder bile is obtained; the tube is then allowed to hang down and the bile to siphon off into tubes of various culture media. The infecting organism usually predominates in these cultures. This author finds that the commonest organism is a coliform bacillus, then a staphylococcus; streptococci, pneumococci, and *M. catarrhalis* have also been found.

Hurst (40) quotes observations of Dr. F. A. Knott on the bacteriology of gall-bladder infections. Pus cells and cholesterol crystals are frequently found in the bile and duodenal contents in these cases. The infecting organism is often grown in pure culture from bile obtained by the duodenal tube. The commonest organism is a coliform bacillus; a streptococcus is only found in exceptional cases.

CHRONIC APPENDICITIS

Like cholecystitis, this may be a secondary metastatic infection, though it not infrequently takes the role of a primary focus in the production of systemic disease. The infecting organisms are most commonly coliform bacilli and streptococci.

INTESTINES

In the search for a focus of infection in a disease such as rheumatoid arthritis, an alimentary infection is often diagnosed on quite insufficient evidence. Just as a tonsil swab will not tell us whether the tonsils be infected, so bacteriological examination of the faeces, without clinical evidence, can give us no information as to intestinal infection. Streptococci, both of the *salivarius* and *faecalis* groups, are normal inhabitants of the intestines. The proportion of streptococci to other organisms in the faeces depends largely on diet and on the rate of passage of the contents along the intestinal canal. A chronic infection of the mucous membrane of the intestine, or of the lymphoid

tissue in its walls, will not be unnoticed clinically. It is possible that organisms from time to time escape from the gut and gain the general circulation, under normal conditions, but in the search for an infective focus the practitioner will be wise to exhaust every possibility before falling back on this. We would lay stress particularly on the difficulty of drawing conclusions from the proportion of streptococci in cultures of the faeces.

FOCI IN THE GENITO-URINARY TRACT

In relation to systemic disease, and particularly chronic arthritis, gonococcal infections are of very great importance. Infective foci in the genito-urinary tract are most commonly of gonococcal origin, though other organisms may be responsible; chronic coliform infection, for instance, is a common condition, but does not often appear to be associated with systemic disease.

ACUTE AND CHRONIC PROSTATITIS AND VESICULITIS

These conditions are most commonly caused by the gonococcus, and are the most important gonococcal foci in the male. Less commonly, prostatitis may be caused primarily by a staphylococcus or a coliform bacillus. The demonstration of the gonococcus in chronic infections may be a matter of considerable difficulty, and the diagnosis must often rest on clinical evidence. In cases suspected of chronic gonococcal infection, the urine and the fluid obtained by prostatic massage should be examined bacteriologically. The urine may contain pus, or more commonly yellow threads which quickly sink to the bottom of the glass, and which are found on microscopical examination to consist of large numbers of pus cells held together by mucus. Films and cultures are prepared from the urinary deposit or from the threads if these are present. The presence of pus cells is certain evidence of infection; but this may be due to staphylococci, streptococci, coliform bacilli, or other secondary invaders. Sometimes the gonococcus, with its characteristic distribution within the pus cells, can be identified with a fair degree of certainty, but

more often bacteriological findings are equivocal. In a Gram film the organism often appears only partially decolorized, while a staphylococcus may be partially decolorized if dead or if technique is faulty. Moreover, certain varieties of staphylococci very closely resemble gonococci in shape. It will therefore readily be understood that a bacteriologist is frequently in doubt as to whether the gonococcus is present or not in these cases. Culture does not help very much; the organism grows with difficulty on special media containing blood or ascites fluid.

The prostatic fluid also should be examined both by direct films and by culture. Normal fluid is an emulsion of fat droplets, with a few epithelial cells. If pus cells are found a prostatitis must coexist. Here again it is not common, in these chronic cases, for the gonococcus to be recognized with any degree of certainty, even though several examinations are carried out. Secondary invaders such as staphylococci, streptococci, and coliform bacilli are often found, but even so the infection may still be primarily gonococcal.

ENDOMETRITIS AND SALPINGITIS

The gonococcus is the commonest primary cause of infection of the genital tract in the female. Chronic foci may be left after acute gonococcal infection, chief of which are chronic endometritis and salpingitis.

In chronic gonococcal endometritis the infection is always mixed, and it is usually impossible to demonstrate the gonococcus; the secondary invaders, staphylococci, coliform bacilli, and others, are generally found.

Inflammation of the endometrium often spreads to the Fallopian tubes. Chronic salpingitis is the ultimate result; it constitutes a most important focus of gonococcal infection in the female.

DISEASES RESULTING FROM FOCAL SEPSIS

ARTHRITIS

The role of focal sepsis in the production of joint disease may be appreciated by a consideration of the following

case of gonococcal arthritis. A baby aged three weeks came under observation with swelling of the right elbow. The history was that two days after birth a purulent conjunctivitis developed; five days later the left foot was swollen; this swelling soon subsided and was followed after four days by swelling of a finger-joint, and this by swelling of the right elbow, mainly from a peri-articular inflammation. Gonococci were demonstrated in the conjunctival pus. Except for splinting the joint, treatment was directed solely to the conjunctivitis. Within a few days of the cure of this localized infection the joint condition cleared up completely.

Theoretically, there are two ways in which joint symptoms arise in such a case. Gonococci may gain the blood-stream and be carried to the joints, there setting up an actual infection. In the case briefly referred to above, the ready subsidence of the joint swelling after disappearance of gonococci from the primary focus suggests a different process. The alternative usually given is that the lesions are due to the action of soluble toxins formed in the primary focus; but hyper-sensitivity of one or more joints is obviously an essential factor. We may postulate that as a result of small quantities of toxin or organisms gaining the blood-stream certain joints become sensitized to this foreign material, and that whenever gonococcus toxin, or gonococci, from the primary focus come in contact with such sensitive joints the changes we call arthritis result as an allergic manifestation.

Two to five per cent. of all patients with gonorrhoea suffer from arthritis. This affords a typical undisputed instance of arthritis resulting from focal sepsis. It may occur during an attack of acute urethritis, pain being the predominant feature and disappearing in a few days. It may complicate chronic gonococcal infections, and in these cases the joint lesions are often indistinguishable from those of the malady we know as 'rheumatoid arthritis'. Rheumatoid arthritis typically affects women in young adult life. Apart from the joint lesions, the general health suffers; the onset is usually insidious, the small joints of the hands and

feet becoming swollen and painful, and the wrists and ankles being similarly affected later. Early, the swelling is almost entirely peri-articular. Other joints may be affected later, and ultimately there may be considerable destruction of bone and cartilage with deformity of the joints. All the evidence points to focal sepsis being an essential factor in the aetiology of this type of arthritis. There would seem to be no evidence that focal sepsis plays any part in the causation of osteo-arthritis or climacteric arthritis.

In rheumatoid arthritis the commonest infective foci are chronic tonsillitis and peri-apical infections. F. G. Thomson (41) states that infection of teeth or tonsils is found in about 75 per cent. of cases. He considers that a secondary focus of infection, namely infection of the intestine, develops in many cases, favoured by the achlorhydria which so often exists in this malady.

The organism responsible in the great majority of cases is probably a non-haemolytic streptococcus.

Specific Treatment of Rheumatoid Arthritis

If the case is seen early, and a focus of infection found and removed, the joint lesions may subside rapidly and even clear up completely. This is not by any means infrequent, and incidentally it demonstrates two points: first, the causal relationship of the infective focus: second, that at this early stage the joints are probably not infected.

When time has been lost by palliative treatment, removal of the septic focus may produce little amelioration in the joint condition. There are two possible reasons for this: either a secondary focus has developed which keeps up the disease process, as for instance infection of a lymph gland, or of the intestines; or the joints themselves have become infected.

Bacteriological examination of the infective focus should always be undertaken and an autogenous vaccine prepared from the predominating organism. In the majority of cases this will be a non-haemolytic streptococcus. In the case of peri-apical infection cultures should be made from the apex of the tooth immediately after extraction, observ-

ing precautions against mouth contamination, which are dealt with elsewhere (see p. 372). In the case of chronic tonsillitis, the tonsils should be sent, wrapped in gauze, to a bacteriologist with as little delay as possible after their extraction. His cultures will be made from the interior of the tonsils after sterilization of the surface.

It is wise to use vaccine treatment in all these cases, whatever the effect of removal of the infective focus. It is not by any means universally accepted that vaccines are of any value in this disorder, but the writers believe that failure is frequently due to incorrect dosage. If it is remembered that the joints are sensitive to streptococci, and that possibly the joint lesions are largely due to repeated reactions to these organisms or their toxins rather than to an actual infection, it will be reasonable to suppose that repeated joint reactions caused by injections of a vaccine may do much more harm that good. The guiding principle in vaccine treatment should be to avoid reactions. One begins, therefore, with a small dose—one million organisms rarely cause any reaction. The dose may at first be increased fairly rapidly in geometrical progression; but if a reaction follows any dose, the next dose should be reduced and the ascent be then more gradual. In any case it will probably be wise to adopt a more gradual increase after a dose of ten millions has been given.

The following scheme may be taken as a guide, but of course no rigid rule can be given. Of an emulsion of ten million organisms per cubic centimetre give the following doses: 0·1 c.cm., 0·18 c.cm., 0·32 c.cm., 0·56 c.cm., 1·0 c.cm. Then of an emulsion of 100 million organisms per cubic centimetre give 0·15 c.cm., 0·22 c.cm., 0·32 c.cm., 0·46 c.cm., 0·68 c.cm., 1 c.cm. It is probably wise after this to make the ascent still more gradual, using an emulsion of 1,000 million organisms per cubic centimetre. Doses should be given at weekly intervals, but the smaller may be given at intervals of four to five days.

If a reaction follows any dose, a course of intravenous injections of 5 per cent. Armour's No. 2 peptone may be given. This appears to have considerable value in prevent-

ing reactions. Warren Crowe (42) recommends the following series of injections:

Day 1	0·1 c.cm.
2	0·2 c.cm.
3	0·4 c.cm.
5	0·8 c.cm.
7	1·4 c.cm.

and then at three or four day intervals

2·0 c.cm.
2·5 c.cm.
3·0 c.cm.
3·0 c.cm.

Between the later doses, an injection of the vaccine may be given. Usually no ill effects follow the injection of Armour's No. 2 peptone. (The preparation of peptone is important: Witte's peptone contains histamins, which may give severe reactions.) Sometimes headache, nausea, or sleeplessness follow, when this treatment should be abandoned. Warren Crowe considered albuminuria a contra-indication.

It is not possible to lay down any rules for the duration of vaccine treatment. The writer's practice is to continue injections for three or four months, and after an interval of three or four months the course is repeated.

In those cases of rheumatoid arthritis which come for treatment after the malady has progressed for months or years, and no focus of infection is discoverable, non-specific treatment only is possible. The great majority of these cases are streptococcal in origin: it is reasonable therefore to attempt immunization with a stock streptococcus vaccine. A useful emulsion is a mixture of *Streptococcus pyogenes* with typical examples of *Streptococcus salivarius* and *faecalis*. Doses are as recommended for the autogenous vaccine.

Treatment of Gonococcal Arthritis

The same principles hold in the treatment of this disorder. Attention is first directed to the cure of the primary gonococcal focus. It is very rarely possible to isolate the

gonococcus responsible, so that if vaccine treatment is employed, a stock emulsion must be used. Reactions are very common, and may be very severe, after injections of quite small doses of gonococcus vaccine. A dose of three million organisms may cause the most severe joint pains. The initial dose should be half a million, or one million, and the increase very gradual. Intravenous peptone is probably of value.

Among disorders of the 'rheumatic' group, fibrositis, myositis, and some cases of neuritis may be results of focal sepsis, though the evidence is not so strong as it is in the case of rheumatoid arthritis.

GASTRIC ULCER

Focal sepsis is probably an important factor in the causation of many cases of gastric ulcer. Rehfuss (43), in discussing this subject, quotes Rosenow's work on the experimental production of ulcers in animals. Rosenow claimed that streptococci could be cultivated from the base of human ulcers: that if animals were injected intravenously with these organisms, duodenal or gastric ulcers of the acute type frequently resulted. He claimed further that such ulcers followed injection of streptococci from infected tonsils or teeth of patients with peptic ulcer, whereas this result never followed injection of streptococci from normal tonsils. Whether these claims be accepted or not, it is certainly true that such septic foci are common in cases of peptic ulcer, and that energetic specific treatment is a logical course.

Rehfuss recommends vaccine treatment for peptic ulcer, in addition to the usual measures, when focal sepsis is discovered.

ANAEMIA AND CHRONIC ILL HEALTH

is a common result of focal sepsis. It is presumably the result of constant absorption of poisonous substances.

MENTAL DISORDERS

It is certainly a reasonable hypothesis that mental disturbance may result from focal sepsis, for there are known

toxic causes of mental change, as, for instance, alcohol and morphine. The conception is, however, hardly more than hypothesis, for it is based only on the coincidence of focal sepsis in many cases, and the improvement, in varying degree, which follows treatment of this in some cases. Dr. P. Watson-Williams (44) discusses the matter in the Semon lecture. He believes that the mild toxaemia may result in mental deterioration, such patients being often labelled neurasthenic. The depression may deepen into melancholia, and may end in delusional insanity.

IRITIS

The commonest cause of acute iritis in men is a gonococcal infection, secondary to infection of the genito-urinary tract. Often a gonococcal arthritis has preceded the iritis; many cases called 'rheumatic iritis' are probably of this nature.

Specific treatment is directed to cure of the primary focus of infection. Vaccines are best avoided, on account of the danger of reactions.

Acute iritis may also occur secondarily to a chronic focus of infection in the nasal sinuses.

Chronic iritis appears to be due to chronic focal sepsis in a large number of instances. Vaccine treatment is often beneficial.

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B. DISEASES OF THE BLOOD

VII. SECONDARY ANAEMIAS.

Anaemia.
Mechanical Anaemia.
Hypoplastic Anaemia.
Toxic Anaemia.
The Effect of Irradiation upon the Blood.

VIII. THE PRIMARY ANAEMIAS, ANAEMIAS ASSOCIATED WITH SPLENIC ENLARGEMENT, HAEMORRHAGIC CONDITIONS, SCURVY, ETC.

The Primary Anaemias.
- Chlorosis.
- Pernicious Anaemia.

Anaemias associated with Splenic Enlargement.
- Splenic Anaemia and Banti's Disease.
- von Jaksch's Anaemia.
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- (Familial) Acholuric Jaundice.

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- Haemophilia.
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Methaemoglobinaemia.
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IX. ERYTHRAEMIA AND LEUKAEMIA.

Erythraemia—
- Secondary Polycythaemia.
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Leukaemia—
- Acute Lymphocytic Leukaemia.
- Acute Myelocytic Leukaemia.
- Chronic Lymphocytic Leukaemia.
- Chronic Myelocytic Leukaemia.

CHAPTER VII

SECONDARY ANAEMIAS

The Normal Blood

The normal blood consists of cells and plasma. **The red blood-cells** number, in an adult man, about 5,000,000 per c.mm. Not infrequently this figure is higher by as much as a million. In women the number is usually lower than that found in men by about 500,000.

The size of normal red cells is about 7·5 μ, and the shape nearly circular.

Immediately after birth the red cell count is found to be raised to the neighbourhood of six million, but falls after about a week to the normal figure, where it remains for the remainder of life, except that occasionally the number is temporarily somewhat greater between the ages of about 6 and 14. Nucleated red cells are occasionally found in the blood soon after birth, but rapidly disappear.

Certain factors, other than those of disease, will influence the red cell count. Life at an altitude is accompanied often by a corresponding erythrocytosis. At 4,000 metres above sea-level the constant increase may be about three millions over the normal, and at lesser heights relatively smaller. Temporary variations occur with fluid changes, especially with that of depletion. Severe vomiting, diarrhoea, sweating, or respiratory loss in hot weather may all cause a definite increase in the red cell count.

The **haemoglobin** figure runs parallel with all these variations in the normal red cell count, but is often lower than the normal 100 per cent. during the first few years of life, when a colour index of 0·7 is not abnormal.

The normal red cells show no abnormalities in staining, local or diffuse, except that about 0·7 per cent. show reticulation by the vital staining method. Such cells are relatively immature.

The **total white cell count** is about 7,500. It appears to vary considerably in the same individual during a twenty-four hour period, and figures varying by as much as 2,000 on either side of this need not be considered abnormal.

In a normal adult the various cells are present in about the following numbers:

Polymorphonuclear leucocytes	5,000 per c.mm.,	65 per cent.
Lymphocytes	2,000 ,, ,,	28 ,, ,,
Large mononuclear leucocytes	300 ,, ,,	4 ,, ,,
Eosinophiles	150 ,, ,,	2 ,, ,,
Basophiles	50 ,, ,,	1 ,, ,,

Both actual figures and percentages are variable to some 10 per cent. on either side. Absolute numbers are the only trustworthy guide in estimating differential blood-counts; as Ehrlich long ago proved, percentages, where the total count may vary up to three times the normal or more, will give often a totally erroneous idea. Both should as a rule be given, but if one only is reported, it should be the absolute number.

The leucocyte count varies in infants and children considerably from the normal. At birth there is a considerable polymorphonuclear increase over the normal figure, frequently as much as 10,000, giving a complete count of 22,000 or so. This polymorphonuclear increase progressively falls and has disappeared by the end of a week, when the fixed figure of about 5,000 is reached, which persists throughout life. The lymphocytes at birth are in excess of the adult figure by about 7,500. This excess becomes gradually less and has as a rule vanished by the age of 5. The decrease is less during the first year or eighteen months than it is later on.

The blood-platelets are in normal individuals present at a figure of about 300,000 to 500,000 per c.mm., or at an erythrocyte-platelet ratio of about 10 to 1.

Normal bloods are of four types as regards compatibility for blood transfusion. The incompatibility of a blood consists in the fact that its corpuscles are lysed by the recipient's serum, thus liberating a foreign protein. The preliminary to such lysis is agglutination, and this property is made use of in determining the group to which such a blood belongs. For further information with regard to compatibility of blood for transfusion, appropriate text-books should be consulted.

ANAEMIA

General Considerations

Anaemia is a condition in which the blood as a whole, or any part of it, is deficient. Clinically, such deficiency is generally taken to refer to the red blood corpuscles or to their haemoglobin content.

Anaemias can be classified in several ways—according to their **cause**, according to the **type of blood picture**, or according to the **degree of reaction** on the part **of the haematopoietic tissues.**

Anaemias whose **cause** is known are described as secondary, in contradistinction to the more mysterious primary class. All anaemias, with the exception of chlorosis, pernicious anaemia, splenic anaemia, and very few others, belong to the former subdivision. With advances in knowledge the adjectives primary, idiopathic, and essential as descriptive of disease will, it is to be hoped, meet their final fate.

According to the blood picture, anaemias are also classified as chlorotic or pernicious in type. The characteristics of the former are: a loss of haemoglobin considerably greater than that of erythrocytes, a low colour index resulting, and a normal or slightly decreased white count; those of the pernicious type are a loss of haemoglobin less than the deficiency in erythrocytes, producing a colour index of above one, a leucopenia and the presence in the smear of nucleated red cells, of polychromatophilia, punctate basophilia, anisocytosis, and poikilocytosis. These latter characteristics are indicative of hurried cell output and of immaturity.

Anaemias of the chlorotic type comprise the majority of those met with, whether the cause be traumatic or toxic. Only when the blood destruction, and therefore the strain upon the bone-marrow, becomes very great, does the latter revert to the foetal type of blood formation and give rise to a blood picture of the pernicious type. Such reversion, or the tendency towards it, as shown by a rising colour index during the course of a severe anaemia with no

corresponding increase in the red cell count or haemoglobin percentage, is of serious prognostic import.

A third subdivision of anaemia is into hyperplastic or hypoplastic anaemias depending upon the **state of reactivity of the bone-marrow.** The maintenance of the normal blood-count, and of course of the haemoglobin cell content, depends upon the permanence of the equilibrium between normal blood formation and normal blood destruction. Anaemia can occur with an increased or with a decreased rate of blood formation. In the former case, blood destruction is at an even more greatly increased rate, and in the latter the rate of destruction may even be normal.

These two types of anaemia are often described as hyperplastic and hypoplastic (or less accurately as aplastic, for a truly aplastic condition would result in death within three weeks). Hyper- and hypoplasia may succeed one another during the course of the same disease.

In hyperplastic anaemias the blood shows evidence of increased erythroblastic activity by the presence in it of an abnormally high percentage of reticulate red cells (the normal being 0·7 per cent.), by anisocytosis, poikilocytosis, polychromatophilia, possibly by punctate basophilia, an increased platelet count and leucocytosis, though some observers regard both poikilocytosis and punctate basophilia as degeneration forms. Any one or more of these characteristics may appear alone or in combination. There is some doubt as to whether the presence of nucleated red cells and of myelocytes indicates an irritated—possibly by some destructive process—or a reacting bone-marrow. Recent authorities hold rather to the former view.

When the blood destruction is sufficiently great, enough bilirubin appears in the plasma to be capable of detection and of quantitative estimation by van den Bergh's reaction. Such a condition obtains in pernicious anaemia, in acholuric family jaundice, possibly in some cases of acute streptococcal septicaemia, and in the anaemias due to the action of certain poisons, such as potassium chlorate, hydrogen sulphide, and trinitrotoluene.

The characteristic of hypoplastic anaemia is that none

of these signs of a reacting haematopoietic system appear. On the contrary the cells, in kind but not in number, are strikingly normal.

In an anaemia of either type prognosis depends upon knowledge of the cause, with the possibility of its eradication, and in determination so far as is possible of the rate of blood destruction and the degree of marrow reactivity, as assessed and compared from time to time.

Clinically, anaemias can best be divided into mechanical anaemias, toxic anaemias, and primary anaemias.

MECHANICAL ANAEMIA

Acute Mechanical Anaemia

This condition occurs most frequently in such conditions as haemorrhage from an external wound, from a gastric ulcer, from a phthisical cavity, from a fibroid, or during parturition. The essential characteristic is that much blood is lost in a short time.

The total volume is suddenly reduced, all of the blood constituents being alike depleted. As a result, the blood picture is unchanged from the normal until time has allowed fluid replacement into the vascular bed. This has generally occurred within forty-eight hours, and with its development the red blood count and haemoglobin percentage both fall progressively. This continued fall must not for the first forty-eight hours be allowed to lead the observer to believe that haemorrhage is necessarily still continuing, the pulse-rate over this period being the better guide. A continued fall, after time for adequate replacement has passed, will naturally suggest further blood loss.

Soon after the haemorrhage has occurred, often within twenty-four hours, there is marked leucocytosis. Simultaneously more red cells than normal will show reticulation by vital staining, and the platelets are increased. In severe cases normoblasts may be seen in the peripheral blood for a few days, but not megaloblasts. These three latter changes all show increased bone-marrow activity, and as a rule are no longer observable after a week.

As stated above, the plasma is the first constituent of the

blood to recover from an acute mechanical loss of blood; its recovery is complete in a few days. The red cell count generally takes four weeks or so to return to normal, and the haemoglobin often as much as eight, or even more, after a severe haemorrhage that has reduced the red cell count by half. The recovery time of course varies directly with the amount of blood lost.

Chronic Mechanical Anaemia

In this condition, small quantities of blood are continuously being lost as a result of some local wound. Haemorrhoids, fibroids, and some cases of gastric and duodenal ulcer provide the most frequent causes.

The blood picture after haemorrhage depends upon the fact that a healthy bone-marrow will respond vigorously to a single large haemorrhage, whereas a bone-marrow repeatedly called upon to supply losses becomes, like the father of a spendthrift, less responsive to successive calls. In the absence of a toxic or constitutional cause the marrow never exhibits more than a certain degree of hypoplasia, the blood picture being maintained at a certain diminished level.

The chief characteristics of this type of secondary anaemia are shown in the following specimen count:

R.B.C.	3,500,000
Hb.	50%
C.I. (Colour Index) . .	0·7
W.B.C.	5,600

The differential white count shows a polymorphonuclear leucopenia and no nucleated red cells. This polymorphonuclear leucopenia is not by any means constant, the white count being sometimes normal. If present, it is suggestive.

The anaemia of carcinoma of the stomach is difficult to place, and though it is certainly due in large measure to loss of blood from the ulcerated surface, it may be due partially to absorption of toxins from the growth itself. As a rule it

is of the chlorotic variety; not infrequently it is of the hyperplastic type, and in the later stages it may in all respects but one simulate pernicious anaemia, from which indeed the history is not dissimilar. Leucocytosis rather than leucopenia is the rule. Moreover, the van den Bergh test does not, as in most cases of pernicious anaemia, show the presence of bilirubin in the blood-serum.

HYPOPLASTIC ANAEMIA

Anaemia occurs either when the normal bone-marrow is replaced by other tissue, as in the leukaemias, in multiple myelomatosis, and occasionally in secondary malignant disease, or when it is injured or destroyed by physical means (X-ray, radium) or by toxins, as in benzol poisoning or in many infective and septic conditions.

These two groups vary from one another in their early stages. In the former group, the invasion of the marrow may temporarily stimulate it to produce nucleated red cells, more reticulate red cells, myelocytes, &c., whereas in the latter group the blood picture is hypoplastic from the start. The later pictures are similar in each type.

The characteristic of a hypoplastic anaemia is a diminution in all the constituents of the normal blood and the absence of abnormal cells. There is no evidence of blood destruction. The red cells are considerably diminished, the haemoglobin being rather more so, giving a colour index of below 1. There is a leucopenia and often a platelet deficiency. In so-called 'aplastic anaemia', these changes are progressive until death, and purpura frequently accompanies the low platelet content.

It is probable that many of the anaemias of infective conditions are due in some degree to a hypoplastic bone-marrow.

In infants suffering from malnutrition and chronic gastro-enteritis a severe aplastic anaemia is not uncommon; it is presumably due to a definite using up of all inherited iron and a lack of iron for assimilation in the food. Treatment with iron intramuscularly is of use.

SECONDARY TOXIC ANAEMIA

Bacterial Toxic Anaemia

Toxins affecting the blood are bacterial or non-bacterial. They may be effective either, as in hypoplastic anaemia, by injuring the bone-marrow, or by producing a haemolysis greater than can be compensated for by this tissue, or lastly, by combining with red blood-cells to such an extent as to produce loss of function in these and anoxaemia of the tissues.

The bacterial causes of toxic anaemia are many; in almost all of these the anaemia is of the chlorotic type.

Septicaemias produce the most severe and progressive anaemia. Repeated haemoglobin estimations will give a very fair indication of the course of the associated toxaemia. Not only is this routine rapid, it is an exact measure of the physiological power of the blood as an oxygen carrier, and, since the haemoglobin loss is as a rule greater than is the red cell deficit, it is the best means of measurement. It, of course, goes without saying that haemoglobin estimations alone give no diagnostic help as to the type of anaemia present. But when the diagnosis is made, a complete blood-count may if necessary be omitted in secondary anaemias in favour of regular repeated haemoglobin determinations. In acute septicaemia, where the patient is reacting strongly (not necessarily successfully), the blood may give evidence of considerable bone-marrow reaction by the presence of myelocytes and nucleated red blood-cells.

Concealed abscesses, of any type, typically empyemata, produce a severe chlorotic secondary anaemia. These chronic conditions are associated more often with a hypoplastic type of blood picture.

In acute rheumatism, articular or cardiac, there is generally a secondary anaemia. This is severe in proportion to the severity of the infection, and its diminution or accentuation corresponds very accurately with the course of the disease; in fact it is probably true that by examination of the chart, haemoglobin percentage, and white blood count, a closer estimate of the activity of the disease in

acute rheumatism can be made than by any other three means.

Pulmonary tuberculosis not infrequently is first manifested by a severe anaemia of the chlorotic type. This is especially true of girls at about the age of incidence of true chlorosis.

A secondary anaemia is fairly often the first severe manifestation of syphilis, especially after the onset of the secondary stage. The anaemia is of the chlorotic type, and the decrease may be to 2,000,000 and 25 per cent. haemoglobin.

In erysipelas there is a slight anaemia. In pneumonia, except in very severe cases, there appears to be very little decrease, and that chiefly in the haemoglobin percentage. In diphtheria there is no anaemia as a rule. In scarlet fever there is a slight secondary anaemia only, but the onset of nephritis or cardiac and rheumatic complications is associated with a considerable increase in its degree. In typhoid fever an anaemia of the chlorotic type becomes more marked as the disease becomes more severe or more protracted. The blood diminution ends with the pyrexia.

In spite of the fashion for finding septic foci it is true that a considerable number of cases of severe secondary anaemia are proved to be due to alveolar abscesses resulting from streptococcal infection. Such cases may show a pernicious type of blood picture. Dental and alveolar sepsis has been invoked as being the actual cause of pernicious anaemia itself. But, though the two often coexist, proof is lacking.

In chronic nephritis, resulting often from an infection, there may be a marked chlorotic anaemia. It is said to add definitely to the gravity of the prognosis in proportion to the degree of anaemia.

Non-Bacterial Toxic Anaemia

The commonest non-bacterial poisons producing secondary anaemias are the metallic and the helminthic. The metallic poisons are lead and mercury, and the helminthic ones are produced by the *Ankylostoma duodenale* and the *Bothriocephalus latus*.

Lead Anaemia. The anaemia of plumbism is a secondary anaemia of the chlorotic type, the haemoglobin deficit being often excessively severe. The white count is normal or may be somewhat increased. The severity of the anaemia depends upon three factors: the dose of lead absorbed, the length of period over which absorption occurs, and the personal susceptibility to lead. The two chief factors are the two last. Usually, the more chronic the condition the more severe will be the anaemia. On the other hand, a person susceptible to lead may after an exposure of a few weeks only during the course of his employment lose as much as 50 per cent. of his haemoglobin.

A feature of lead anaemia is the evidence of reaction on the part of the bone-marrow. Normoblasts are often seen, punctate basophilia is so frequent as to be characteristic, polychromatophilia and anisocytosis are common.

The other laboratory findings in plumbism are urinary: albuminuria, and the presence of lead. Albuminuria of some degree is present in almost every case of recent lead toxaemia. Its absence is evidence against recent plumbism. There are at this early stage no other evidences, as a rule, of renal damage than a few hyaline and granular casts, unless the exposure has been to sociological rather than to industrial doses. In that case epithelial casts may be found. Chronic plumbism, after years of exposure, is often succeeded by chronic nephritis and arteriosclerosis. The urinary changes are characteristic of these latter conditions. Lead is excreted in the urine in probably every case of plumbism, but the amount is small and the quantitative investigation long and laborious. In medico-legal cases its presence or absence may be a matter of necessary proof.

Mercurial Anaemia. This condition does not usually follow the ingestion of ordinary doses of mercurial salts, but it may result when exposure has been to poisonous doses. The anaemia is of the chlorotic type like that of lead, but it differs in not showing punctate basophilia or the presence of nucleated red cells to an identical degree.

Helminthic Anaemias. *Ankylostoma duodenale*, or its cousin *Necator americanus*, produces a secondary anaemia

as a result of the local trauma and ulceration of the duodenal mucosa, possibly also to some extent by means of a haemolytic toxin. The resulting anaemia is characteristically of the chlorotic type. Evidence of bone-marrow reaction, in the form of nucleated red cells, myelocytes, polychromatophilia, anisocytosis, &c., may be present. A characteristic but not constant finding is the presence of an eosinophilia. This in a severe anaemia should always suggest a possible parasitic origin. The eosinophilia may be of a high figure, even up to 20 or 30 per cent., but it does not as a rule exceed 10 per cent. (See also p. 178.)

Other Pathological Findings

The stools always contain evidence of the disease in the presence of ova. Three examinations by a pathologist who used a concentration method should exclude or prove their presence.

After anthelmintic treatment two proceedings should be undertaken: (1) an examination of the stool for the worms; (2) after a week's interval to allow of their return to health, if still unexpelled, further examination of the stool for ova to prove that no more parasites remain. They are usually present in numbers greater than one.

Bothriocephalus latus may produce an anaemia of the chlorotic type, but is more famed for giving rise to a blood picture indistinguishable from that of pernicious anaemia. The disease is only common in certain countries, for example Russia, but should be thought of in the presence of an eosinophilia. This finding is not absolutely constant. The patient's stools contain the ripe proglottides and the ova. After anthelmintic treatment the head of the parasite should be found, to prove the reality of the cure. (See also p. 178.) The ova of this worm are more numerous in the stools than are those of *Taenia solium* or *Taenia mediocanellata*.

ANAEMIAS IN METABOLIC DISEASES

Two diseases associated with metabolic abnormalities are frequently accompanied by an anaemia. In rickets an anaemia is frequent, and is of the chlorotic type and varies

with the course of the disease. The clinical condition described as von Jaksch's anaemia is sometimes associated with rickets.

In myxoedema a moderate secondary anaemia is the rule; it is of the chlorotic variety, and signs of bone-marrow reaction are usually absent. Leucopenia is common. Less commonly a really severe anaemia is the cause of the symptoms that bring the patient for advice. So marked are the changes sometimes that pernicious anaemia may be suspected, for the polymorphonuclear leucopenia is not infrequent, and in an advanced case the colour index approaches unity.

It is uncertain to what extent malignant neoplasms, apart from questions of haemorrhage, secondary infection, or bone-marrow destruction, can give rise to a 'cachectic' secondary anaemia. In some cases it would seem that this occurs. When the above factors can be ruled out the degree of anaemia, usually chlorotic in type, increases with the advance of the disease. Punctate basophilic staining of the erythrocytes is not uncommon in the anaemia accompanying carcinoma, normoblasts are occasionally found, and megaloblasts have been described.

THE EFFECT OF IRRADIATION UPON THE BLOOD

The published accounts of the effect of X-rays and of radium upon the blood are misleading; this is chiefly due to the incomplete statements made as to the exact dosage used. Certain facts, however, appear to be sufficiently well substantiated (1).

Radium has an action similar to that of X-rays, but it is in all respects milder.

Two types of individual are affected by exposure to X-rays, the worker in an X-ray department and the patient treated by irradiation. The former is rarely affected to any extent owing to the efficacy of the usual precautions taken, but the changes, if they occur, are due to a hypoplasia of the blood-forming tissues. They are:

I. Leucopenia.
II. Slight Secondary Anaemia.

The **leucopenia** affects the lymphocytes to the greater extent, but also slightly the polymorphonuclear cells. Owing to the variation that occurs throughout the day in normal people, the counts should be made at the same time of day if deductions are to be made from their comparison, for the diminution in the white cell count in irradiation, though progressive, is slow. A **secondary anaemia** is a rare occurrence.

In the case of patients treated by X-ray, the symptoms produced by X-ray administration, and termed 'X-ray sickness', do not correspond in degree with the changes produced in the blood-count.

When such changes occur the cells chiefly affected are in order:

I. The Lymphocytes.
II. The Polymorphonuclears.
III. The Red Blood-cells.

Lymphocytes. A single dose of the size usual in deep X-ray therapy will produce a leucopenia, chiefly by its action upon the lymphocytes. It reaches its lowest point in about six days, this being generally in the neighbourhood of 5,000 per c.mm. Recovery occurs in about 9–28 days. Subsequent intercurrent doses will reduce the count still further and will postpone the return to normal figures, the lymphocytes being kept at a low figure. It is probably true that a dangerous depression of the haematopoetic tissues is not to be feared if at the commencement of treatment the white blood count was normal, and if signs of hypoplasia of the bone-marrow are absent; these are a fall in the actual numbers of granular white cells, a fall in the platelet count, and a fall in the number of reticulate red cells.

Polymorphonuclears. Irradiation is usually followed within forty-eight hours by a polymorphonuclear leucocytosis of a greater or a lesser extent. No deductions can be drawn from its presence.

An anaemia is rare after X-ray therapy, though it may follow excessive doses. Dangerous damage can be done to the blood-forming tissues in the absence of an anaemia.

Erythema doses of X-rays have been found to produce lymphocytosis and an increased platelet count (2).

CHAPTER VIII

THE PRIMARY ANAEMIAS, ANAEMIAS ASSOCIATED WITH SPLENIC ENLARGEMENT, HAEMORRHAGIC CONDITIONS, SCURVY, ETC.

CHLOROSIS

Though chlorosis is the classical prototype of the majority of the anaemias, as a primary disease, it is becoming progressively rarer.

The cause is unknown. As a result of the presence of some pathological cause or of the absence of some physiological necessity the following changes occur :

Blood-volume is increased.

Haemoglobin is greatly decreased.

The red cells are somewhat diminished. Nucleated or otherwise immature red cells are not usually found.

The white cell count is unchanged or slightly diminished.

There is no great evidence of marrow reaction.

Platelets may be somewhat increased.

The abnormalities can be most readily explained on the assumption that the bone-marrow has been rendered hypoplastic by some unknown cause.

The presence of polychromatophilia, poikilocytosis, normoblasts, myelocytes, or other evidences of marrow activity in an anaemia suggests a definite discoverable cause and makes chlorosis an unlikely diagnosis.

Haemoglobin estimations, once the diagnosis is made, offer the most accurate means of measuring the progress of the disease. The low haemoglobin percentage is shown in the film by the presence of a central clear area in many of the cells, producing the characteristic pessary or ring forms.

A typical blood-count would be :

R.B.C.	4,000,000
Hb.	35 %
C.I.	0·44
W.B.C.	7,000 (proportions normal).

Well-marked pessary staining of the red blood-cells is present. No abnormal cells seen.

PERNICIOUS ANAEMIA

Pernicious anaemia is a condition in which, as a result of some unknown cause producing great destruction of red blood-cells, the bone-marrow reverts to a foetal type of blood formation. Dental sepsis is common and, in alliance with the frequent achlorhydria, has been accused of producing the disease by intestinal insemination of haemolytic streptococci. Of this process there is no convincing evidence.

The usual Pathological Findings are :

I. Diminution in the Red Cell Count.
II. A lesser Diminution in the Haemoglobin Percentage, producing a colour index of above unity.
III. A Leucopenia.
IV. The red blood-cells show Poikilocytosis, Anisocytosis, Polychromatophilia, and Punctate Basophilia to a greater or lesser extent.
V. Megaloblasts as well as normoblasts are often found in the circulating blood.
VI. The blood-serum gives a Positive Indirect van den Bergh's Reaction.
VII. The Gastric Juice frequently contains no free Hydrochloric Acid.

The essential characteristic of the disease is excessive blood destruction, and this, as in other haemolytic anaemias, is manifested by the presence of bilirubin in the blood-plasma, as shown by **van den Bergh's test**. Quantitative estimation of the amount present, as measured in units, gives from time to time information as to the rate of destruction of red cells. This alone is not sufficient to enable the formation of an immediate prognosis: in addition the rate of blood formation as deduced from evidences of bone-marrow activity should be considered.

The presence of a positive van den Bergh's test in a case of suspected pernicious anaemia is of very considerable value in diagnosis; a negative result is of definite but of lesser value.

The abnormal type of bone-marrow reaction is proved by the presence of genuine **megaloblasts** in the blood films. Should the red cell count be near the 3,000,000 figure they may not be present, but in counts near 1,000,000 they are to be found, often after a search of several films, in nearly every case.

Normoblasts are frequently seen. The idea that a blood crisis, or the sudden increase of the number of nucleated red cells in the blood, indicates a temporarily successful bone-marrow response is now disputed. Rather is such a phenomenon regarded as a sign of severe marrow destruction. It is certainly true that in cases progressing steadily to a fatal issue, or in cases nearing that event, the phenomenon is common.

The signs that would seem to be most reliable in assessing bone-marrow reactivity are the platelet count, the reticulate red cell count, and the leucocyte count. These are all three diminished in proportion to the aplasia and increased in proportion to the hyperplasia of the bone-marrow. The normal platelet figure is about 500,000 per c.mm., and the normal reticulate red cell count about 0·7 per cent. Signs of hyperplasia suggest always the possibility of remissions; indeed, a greatly though temporarily increased reticulocyte count characteristically occurs during the early days of successful liver treatment. The type following pregnancy is generally of the hypoplastic variety.

The **red cell count** varies greatly. During a remission it may be of the normal figure, and during an exacerbation it may fall to below a million. It is unwise to diagnose pernicious anaemia with the red cell count above 3,000,000. The colour index should be enumerated carefully in a case of severe anaemia. Accurate haemoglobinometers should be used in estimating a fact of considerable prognostic import. Haldane's or Sahli's apparatus are both reliable. The presence of megaloblasts, except in myelocytic leukaemia, indicates pernicious anaemia in the vast majority of adult cases. Their absence does not exclude pernicious anaemia.

Punctate basophilia is common in the red cells, as are also abnormalities in their size and shape.

A **polymorphonuclear leucopenia** is present in nearly every case. The much-vaunted lymphocytosis does not occur. It is fictitious and is due to the habit of counting in percentages rather than in actual figures. Leucocytosis, on the other hand, suggests an anaemia of the pernicious type, but due to some other, probably discoverable, cause. A white count of over 9,000 makes uncomplicated pernicious anaemia unlikely, one above 12,000 practically excludes it. The severer the leucopenia the severer is the hypoplasia of the bone-marrow as a rule. The reverse of this also holds.

Leucocytosis, as a response to some secondary infection, such as pneumonia, frequently does not occur in this disease. The presence of myelocytes indicates disintegration of the marrow and probable loss of reactivity, rather than a tendency towards remission.

Transfusion in pernicious anaemia acts in two ways. The bone-marrow appears to receive a temporary stimulus, and blood-volume is for the time to some extent renewed. The first of these is the more important result. The bone-marrow response, if it is to come, will appear within two weeks after the transfusion, and the red blood count may continue to return towards the normal figure, which indeed in favourable cases it may reach. The colour index, however, frequently remains above 1. Simultaneously the normal leucocyte count may be attained. Regular haemoglobinometer readings should be taken, failing complete blood-counts, as the most accurate guide to the immediate prognosis. If further and more accurate evidence be needed as to the amount of regeneration it can be sought in the platelet count, the reticulate red cell count, and the white blood count.

Other laboratory findings are achlorhydria and albuminuria. The stools, moreover, should always be examined three times for the ova of parasites in patients who can conceivably have been exposed to ankylostomiasis or to bothriocephalus infection.

The **gastric achlorhydria** is so common as to be of some diagnostic value. Its presence is evidence in favour of the disease and its absence the converse. Neither finding is, of

course, conclusive alone. It must be remembered that absence of free hydrochloric acid in the stomach is also a feature of carcinoma of that organ, a disease that may simulate pernicious anaemia closely. The absence of occult blood from the stools would in a severely anaemic patient be evidence against carcinoma of the stomach.

Pernicious anaemia gives blood films that are very suggestive, but the diagnosis cannot be made from films alone sent by post to a laboratory. Such a practice is both unsound scientifically and dangerous.

A typical blood-count would be:

R.B.C.	1,800,000
Hb.	40 %
C.I.	1·1
W.B.C.	3,000

The film shows 2 megaloblasts, 1 normoblast, and 6 myelocytes in counting 300 white cells. The stained film shows an anisocytosis, poikilocytosis, polymorphonuclear leucopenia, and polychromatophilia, all well marked. A few red cells show punctate basophilia.

The combination of a colour index greater than unity and a leucopenia is strongly suggestive of pernicious anaemia. The additional presence of megaloblasts is practically diagnostic.

Treatment

Minot and Murphy (3) have recently introduced the liver diet for the treatment of pernicious anaemia. Should an adequate quantity be taken, a progressive improvement in the blood picture takes place. The amount they suggest is 300 grammes per diem.

The following changes take place in the blood picture:

I. An Increase in Reticulocytes.
II. A progressive Increase in the Red Cell Count and Haemoglobin Percentage.
III. A Diminution in the Blood Bilirubin.
IV. Disappearance or Diminution in the Leucopenia.
V. A Disappearance of Abnormal Red Cells, both nucleated and non-nucleated.

The **increase in the reticulocytes** from their normal figure of about 0·7 per cent. to a figure in the neighbourhood of 15 per cent. is first evident after three or four days, is maximum at about the seventh day, and disappears about the twelfth. It is of considerable prognostic importance, for its height is generally proportional to the rate of red cell recovery. In certain cases it is so transient that, where that information is required, daily blood films should be examined over this period.

The reason for the rise is possibly as follows: In pernicious anaemia there is a weakness in the developmental link connecting the normoblast with the mature erythrocyte. This weakness is apparently overcome by the liver diet. Consequently there is at first a flood of young reticulocytes, which, as production becomes attuned to the normal level, becomes rapidly less, although the regenerative process still progresses.

The **increase** in the **red cell** and **haemoglobin values** and the **disappearance** of the **leucopenia** and the **abnormal red cells** need no further comment.

The **diminution in the blood bilirubin** is best followed by the quantitative indirect van den Bergh test. It is proportional to the diminution of haemolysis and to the increase in the red blood-cell and haemoglobin values. The normal figure is generally below 0·5 of a unit. In pernicious anaemia the figure is frequently above 1·0 unit. During remissions the normal figure may be reached, and during exacerbations readings of 2·0 may occur.

ANAEMIAS ASSOCIATED WITH SPLENIC ENLARGEMENT

SPLENIC ANAEMIA AND BANTI'S DISEASE

Splenic anaemia is probably due to the combined effect of slight blood destruction and slight hypoplasia of the bone-marrow. Generally, the rate of destruction is not sufficient to give a positive van den Bergh's test for bilirubin in the blood greater than the normal; evidence of the hypoplasia is seen in the leucopenia and the comparative rarity with which nucleated red blood-cells, or abnormalities

in the shape of red cells, appear during the course of the disease.

As is the case with most severe chronic anaemias, periods may occur during which, corresponding presumably to some diminution in the amount of toxin present, the marrow responds more vigorously by the temporary production of such cellular evidences of regeneration.

The cause of the disease seems to be largely resident in the spleen, for removal generally brings about a cure.

Pathological Findings

The typical pathological findings are an **anaemia of the chlorotic type** and a **leucopenia**. The film shows no great abnormalities other than occasionally a few normoblasts or myelocytes. Poikilocytosis, anisocytosis, and polychromatophilia are not usually present until the later stages of the disease. The leucopenia involves all of the white cells, but more particularly the polymorphonuclear cells. There is no increase in the fragility of the red cells.

In the later stages of the condition cirrhosis of the liver appears, and it is to this symptom-complex that the name Banti's disease is properly applied. To the picture of a severe anaemia of a definite type are added eventually signs of hepatic inadequacy and jaundice. (See p. 225.)

The earliest of the pathological findings may be the leucopenia; this is closely followed by a diminution in the haemoglobin content, and later by an erythropenia. The whole course of the disease may be spread over many years.

A typical blood-count would be:

(1) *Early.*	R.B.C.	3,500,000	The leucopenia is chiefly polymorphonuclear. One normoblast seen in counting 300 white cells. No abnormality of size and shape of red blood-cells.
	Hb.	42 %	
	C.I.	0·6	
	W.B.C.	3,500	
(2) *Late.*	R.B.C.	1,500,000	The leucopenia is chiefly polymorphonuclear. Ten normoblasts and 15 myelocytes seen in counting 300 white cells. Slight poikilocytosis and anisocytosis are present.
	Hb.	20 %	
	C.I.	0·7	
	W.B.C.	1,800	

VON JAKSCH'S ANAEMIA,

or

ANAEMIA PSEUDOLEUKAEMICA INFANTUM

The above titles have been given to a disease, possibly of a varying aetiology, whose chief characteristics are its occurrence in infants, splenomegaly, and a blood picture of a characteristic type. The individuality of the condition is probably dependent upon the constancy to type of the reaction of the haematopoietic tissues to unknown causes, among which are possibly included malnutrition, rickets, and congenital syphilis. Cases, however, often occur in the absence of evidence of any such causes.

The blood picture shows evidence of very considerable marrow activity. That this occurs is borne out by post-mortem evidence. It is to be presumed, therefore, that considerable blood destruction is simultaneously in progress. Knowledge as to the result in this disease of van den Bergh's test as showing the presence of bilirubinaemia is, however, at present lacking.

The Common Pathological Findings are as follows :

The **red cell count is very greatly reduced;** figures around the neighbourhood of 1,000,000 are common. The drop is frequently quite rapid.

The haemoglobin is simultaneously and more considerably reduced, giving as a rule a colour index of under unity. Simultaneously, there are thrown into the blood-stream very considerable numbers of red nucleated blood-cells. The shortness of the period between foetal life and the age at which the disease occurs appears to permit of an easier reversion, on the part of the bone-marrow, to a foetal type of activity, than is usual in adults. These nucleated red cells are largely normoblasts of a variety of kinds, but also frequently include a considerable number of megaloblasts. The presence of megaloblasts in severe secondary anaemias in infants bears no relation to the severity of the prognosis.

The erythrocytes show generally anisocytosis, poikilocytosis, and polychromatophilia.

The **white cells** generally show a considerable **increase.** This is as a rule to more than 20,000 and not infrequently to as high as 40,000. It involves all the types of white cells, but is more marked in the polymorphonuclear count. Neutrophile myelocytes are usually present and frequently occur in large numbers.

Transfusion intramuscularly or intravenously of blood appears to have a remarkably stimulating effect on the erythropoietic tissues. In the former case blood-typing is not necessary.

A typical blood-count would be:

R.B.C.	1,200,000	In counting 300 white cells, 6 megaloblasts, 10 normoblasts, and 20 neutrophile myelocytes were seen. Many of the erythrocytes showed poikilocytosis, anisocytosis, and polychromatophilia. The leucocytic increase was largely polymorphonuclear, but involved to a lesser extent the lymphocytes and large mononuclear cells.
Hb.	20 %	
C.I.	0·8	
W.B.C.	35,000	

GAUCHER'S DISEASE

To describe this disease as a subtype of splenic anaemia is to ignore completely the remarkable individuality of its splenic histology. As a result of some unknown stimulus, the spleen becomes filled with large cells, often 40 μ in diameter, similar to endothelial cells and possibly derived from the reticulo-endothelial system.

Later in the disease the liver becomes infiltrated, and finally parts of the bone-marrow.

The Pathological Findings are: I. The presence of the typical cells in material obtained by splenic puncture, where this procedure appears justifiable. II. A slight secondary anaemia of the chlorotic type. III. A leucopenia.

Nucleated red cells, abnormalities in the size and shape of the red cells, and myelocytes are generally absent.

The leucopenia, if present, involves chiefly the polymorphonuclear cells.

Van den Bergh's reaction in one observed case was negative.

(*FAMILIAL*) *ACHOLURIC JAUNDICE*

As a result of some tendency, frequently though not invariably inherited, the red blood-cells are unusually fragile. The result of this is seen in a brownish discoloration of the skin and in the presence of a mild anaemia of the chlorotic type in cases of long standing.

Pathological Findings

These are:

I. Evidence of Increased Fragility of the Red Blood-cells.
II. Evidence of Blood Destruction.
III. An Unusually High Reticulocyte Count.

The constant and the most valuable finding, as regards diagnosis, is the **reduction of the resisting power of the red blood-corpuscles** when exposed to sodium chloride solutions of varying strengths. A sample of normal blood undergoes complete haemolysis in a solution of 0·35 per cent.; as the strength of the solution is increased an increasing number of cells resist, until at 0·45 per cent. no evidence of lysis is found.

The blood of the patient with acholuric jaundice consists of cells which will all become lysed in solutions of a higher percentage than 0·35, generally about 0·45 per cent., and some cells will become lysed up to a percentage of 0·6 or 0·7 per cent.

This fragility is present throughout the disease, and upon its presence diagnosis depends. Variations in it will be a guide as to the rate of blood destruction occurring in the body. It disappears after splenectomy.

Evidences of blood destruction are to be found in the secondary anaemia and the bilirubinaemia.

The anaemia is not invariable, and when present it indicates as a rule that the disease is of long standing. It is less severe in the familial than in the sporadic cases, and in the latter sometimes becomes temporarily much more profound in the form of a 'crisis'. Though generally of the chlorotic type, it may in advanced cases revert to the perni-

cious picture, with a corresponding increase in the severity of the prognosis.

The bilirubinaemia is proved by van den Bergh's test, and a series of quantitative results will give an indication as to the rate of haemolysis.

Evidences of blood regeneration are to be found in increase in the reticulate red cells, and possibly in anisocytosis and poikilocytosis.

The reticulate red cells as determined by vital staining are greatly increased, 15–20 per cent. being a not uncommon figure. There is very considerable variation in the size of the red cells from the normal. The average diameter is definitely diminished. They also show well-marked poikilocytosis and anisocytosis. Polychromatophilia is not uncommon.

Normoblasts and a few myelocytes are found in the later stages. Megaloblasts have been described as occurring there also.

The leucocyte count is variable. It provides a means of estimating the haematopoietic powers of the bone-marrow, lower figures corresponding to hypoplasia and vice versa.

HAEMORRHAGIC CONDITIONS

Purpura { Secondary. / Primary.
Haemophilia.

SECONDARY PURPURA

Like anaemia, purpura is a symptom. Secondary purpuras form a growing class whose number is likely to become extended as the causes of the idiopathic purpuras become known. Secondary purpura accompanies known diseases that entail a reduction of blood platelets, such as pernicious anaemia or 'aplastic' anaemia in their later stages, or diseases that are associated with toxic or bacterial damage to the arterioles or capillaries, as is the case in septicaemia.

Other examples of the first class are benzol poisoning, diphtheria, and miliary tuberculosis, where apparently the platelet-forming centres of the bone-marrow are depressed by the toxin, and lymphatic leukaemia in which they are mechanically crowded out. These can be described as secondary purpura haemorrhagica, for haemorrhages from various sources occur frequently, and the platelets, as in 'idiopathic purpura haemorrhagica', are greatly diminished in number.

Examples of the second are septic endocarditis, streptococcal septicaemia, meningococcal meningitis, and many others.

Similar local injuries may be due to a toxin or drug. This is the case with iodides, chloral, copaiba, mercury, arsenic, and quinine: also with snake venom.

Old age and chronic wasting conditions are also often associated with purpura, as are rarely nerve lesions, such as herpes and tabes.

In none of the members of this second class of secondary purpura are the blood platelets diminished to any extent.

PRIMARY PURPURA

Purpura Haemorrhagica ('Essential Thrombopenia').
Purpura Simplex.
Henoch's Purpura.
Schönlein's Purpura (*Peliosis Rheumatica*).

PURPURA HAEMORRHAGICA ('ESSENTIAL THROMBOPENIA').

Purpura haemorrhagica is a condition in which, as a result of severe platelet deficiency, the bleeding time is greatly prolonged.

That this is an incomplete explanation is proved by the fact that the amount of bleeding is by no means directly proportional to the extent of the platelet diminution, and that even in the face of an extensive decrease, bleeding may not occur. Clotting time *in vitro*, as opposed to the patient's bleeding time, is often normal in severe thrombopenia.

But the clot is very abnormal and characteristic, being non-retractile and less adherent than normal.

The low platelet count, however, is the characteristic finding in this particular type of purpura. In the absence of some known cause, such as extensive bone-marrow destruction or hypoplasia, it assumes the dignity of a disease.

It is not clear why in purpura haemorrhagica there should be a platelet deficiency. The bone-marrow in most cases shows no tendency to stint the production of the other cellular elements arising from it, the concomitant anaemia being apparently directly due to the mechanical blood loss. In a few rare cases of 'aplastic anaemia' there are both thrombopenia and severe purpura, but evidence is not available for the linking up of the two conditions and for explaining purpura haemorrhagica as being a state in which as a rule the platelet-forming centres of the marrow only are affected. It is possible that the deficiency is due to a continuous and over-active removal of platelets from the circulation on the part of the reticulo-endothelial system or some other mechanism. But there is no clear evidence for either hypothesis.

Pathological Findings

I. Platelet Deficiency.
II. Prolonged Bleeding Time.
III. Secondary Anaemia.

The **platelet deficiency** and the amount of bleeding roughly correspond, but by no means accurately. Generally, an improvement, or the reverse, in the clinical condition is accompanied by an increase or decrease in the platelet count.

The normal number of platelets is generally taken to be about 400,000 per c.mm., and the variation may be to the extent of 100,000 upon either side of this figure. Moreover, it must be remembered that even in the hands of a pathologist used to counting platelets the experimental error is often as high as 10 per cent., and allowances should be made to that extent in assessing results. When the fall

is to around the figure of 50,000 haemorrhagic symptoms are likely to occur. In purpura haemorrhagica the count is often in the neighbourhood of 15,000. The more acute the case the greater the deficiency as a rule, the chronic cases having less reduced counts. The **bleeding time** is prolonged in all cases and most markedly in the acute cases. The clot is characteristically non-retractile.

The **secondary anaemia** is typical of that following mechanical haemorrhage. The more acute the loss of blood the greater as a rule is the tendency towards the appearance of signs of marrow reactivity, such as the presence of an increase in the reticulate red cells, anisocytosis, slight poikilocytosis and slight polychromatophilia, and a leucocytosis. In the more chronic cases these signs of marrow response become less, and leucopenia is not infrequent.

Differential Diagnosis

The diagnosis depends upon the exclusion of purpuras due to some well-recognized cause, such as leukaemia and septicaemia, and upon the platelet count of the blood. In other types of purpura, though there may be some reduction in the count, this is never to the marked extent typical of this condition. In scurvy the platelets are rarely reduced to any extent, in which condition also a lymphocytosis is common.

Treatment

Transfusion is of use as a means of meeting the crisis produced by severe blood loss; it appears to have no permanent effect upon the course of the disease. Splenectomy in essential thrombopenia is followed in a reasonably high proportion of cases by a cessation of bleeding and a return of the platelet count to the normal figure. For discussion as to the justifiability of the operation, search must be made in appropriate text-books.

PURPURA SIMPLEX, HENOCH'S PURPURA, SCHÖNLEIN'S PURPURA (*Peliosis Rheumatica*).

The close relationship of these three conditions is proved by the fact that though they often occur as isolated clinical entities, yet they may succeed one another in the same patient. The underlying cause of the purpura is probably similar, if not identical in all three types.

The essential lesion is probably a local one of the capillaries or arterioles, and is presumably of toxic origin. That the underlying cause may in some cases be of an infective nature is suggested by the not infrequent association with the disease of tonsillitis, acute rheumatism, and acute nephritis.

Henoch's Purpura is the name given to the association of a cutaneous with an intestinal lesion. The latter occurs as a local haemorrhagic condition, bleeding occurring into the sub-mucous and sub-peritoneal areas of the intestine, accompanied by great local congestion. Three sets of symptoms and signs result from this: (i) the presence of considerable colic; (ii) signs of partial intestinal obstruction, vomiting, and diminished passage of faeces; (iii) bleeding from the intestinal surface. The blood may be more or less coagulated, and is not as a rule much intermingled with mucus.

Schönlein's Purpura is the label given to the condition where cutaneous purpura is accompanied by pain and even swelling of the joints. Its close association with acute rheumatism is shown by the synonym 'peliosis rheumatica'. The joint swelling is chiefly synovial, but effusion occurs. Schönlein's disease is more frequently associated with tonsillitis, acute rheumatism, and acute nephritis than are the other types of purpura; and the clinical pathological findings of these conditions are present in many cases.

There appears to be a fairly regular gradation between purpura on the one hand and anaphylactic phenomena upon the other, the intermediate steps being peliosis rheumatica, erythema multiforme, and intermittent hydrarthrosis.

Pathological Findings

I. The blood platelets are not diminished to the extent seen in purpura haemorrhagica. They may be normal in number or at the most diminished by half.

II. There may be a slight secondary anaemia of the chlorotic type.

III. There is no change in the leucocyte count in purpura simplex; in Schönlein's purpura there is some leucocytosis which, if definite symptoms and signs of active rheumatism coexist, will show a corresponding rise. In Henoch's purpura the amount of leucocytosis probably varies with the amount of blood extravasated into the wall of the gut. In some cases the figures may be above 20,000.

HAEMOPHILIA

This disease, 'an inherited tendency for males to bleed', is apparently due to some abnormality in the action of the blood platelets during the process of clotting. The clotting time is greatly prolonged, as is therefore the bleeding time, but the clot when formed has the normal consistency. It is uncertain whether the defect is in the thrombokinase or in connexion with some not understood property of the platelets associated with clotting.

Pathological Findings

I. Coagulation time is greatly prolonged.

II. Bleeding time is similarly prolonged.

III. The Platelet Count is normal and after a haemorrhage often increased.

The blood-count, except after bleeding, when it shows the changes characteristic of mechanical haemorrhage, is normal in total and differential counts.

Transfusion, apparently by temporarily adding a number of normal platelets, is of use as an aid to stop bleeding. Certain observers claim that monthly intramuscular transfusion of 15 c.cm. of whole blood has eventually removed

the bleeding tendency. There is some doubt as to the value of this procedure.

The production of an allergic reaction in a haemophilic will often reduce the bleeding time very considerably (4). This reduction does not last longer than a week, but may be of use if tooth extraction or some other surgical operation is contemplated. The bleeding time should be carefully estimated, to prove whether the desired shortening has in the particular case been obtained.

The original sensitivity is produced by the injection intravenously, with all proper care regarding dilution by half in normal saline and very slow injection of the first few cubic centimetres, of 10 c.cm. of horse serum. After an interval of 12 days, 1 or 2 minims of horse serum are injected intradermally. This produces a very slight local and general reaction, and simultaneously an allergic state, during which the bleeding time is shortened. A second and third intradermal injection will re-create the state when required.

SCURVY

The Pathological Findings in adult scurvy are:

I. A Prolonged Bleeding Time but a Normal Coagulation Time.

II. A Secondary Anaemia, generally severe, of the Chlorotic Type with a Leucocytosis.

III. No Diminution in the Platelet Count below about 300,000.

The anaemia is in proportion to the severity of the attack.

In infantile scurvy a severe anaemia is rare, and the blood-count, as regards cells and platelets, is normal.

As a rule, red blood-cells are present in the urine.

METHAEMOGLOBINAEMIA

The absorption of acetanelide, veronal, sulphonal, trional, plasmochin, phenacetin, and the nitrites may under certain conditions cause a partial methaemoglobinaemia.

The Pathological Findings are:

I. The presence of a Methaemoglobin Spectrum in a sample of blood laked in distilled water and ex-

amined spectroscopically (or in the transilluminated ear lobe).

II. In certain cases also evidence of Methaemoglobinuria.

III. The Blood-count is Normal.

SULPHAEMOGLOBINAEMIA

Sulphaemoglobinaemia is a rare condition, due, apparently, to the absorption from the intestine of sulphuretted hydrogen, and to the action of this upon the haemoglobin.

The Pathological Characteristics are:

I. A Methaemoglobinaemia: as proved by spectroscopic examination of blood laked in distilled water, or even by spectroscopic examination of the transilluminated ear lobe.

II. The Presence of a 'Nitroso-bacillus' in the Buccal Saliva of the patients.

The **methaemoglobin** is distinguished from sulphaemoglobin by the fact that the addition of ammonia immediately removes the absorption band from the spectrum of the former but not of the latter from the laked blood.

The **nitroso-bacillus** is not the direct source of the sulphuretted hydrogen, but, by its reducing power on the haemoglobin, would seem to render the latter ready to absorb from the intestine what hydrogen sulphide was at the time available.

The blood may show a slight secondary anaemia or may be normal in other respects.

CARBOXYHAEMOGLOBINAEMIA

Coal-gas poisoning is the commonest cause of carboxyhaemoglobinaemia. The pathological finding of importance is the detection of the characteristic absorption bands in the spectrum of the blood. The amount of blood necessary for its detection and estimation is small, half a cubic centimetre of oxalated blood being sufficient. In fatal cases the saturation percentage is generally over 60. Recovery can occur with a saturation of 50 per cent. The saturation percentage can be read by a special spectroscopic method.

CHAPTER IX

ERYTHRAEMIA AND LEUKAEMIA

ERYTHRAEMIA

I. Secondary Polycythaemia.
II. Polycythaemia Rubra Vera
(Erythraemia. Vaquez' Disease).

SECONDARY POLYCYTHAEMIA

Secondary polycythaemia may be relative or absolute. A relative increase in the red cell count is produced by dehydration. Severe diarrhoea or excessive sweating appears to be the commonest cause. A compensatory polycythaemia accompanies conditions in which the blood is only partially aerated. In some forms of morbus cordis the venous blood is not submitted in its entirety to the pulmonary circulation; also in certain forms of respiratory disease, particularly emphysema, there is considerable alveolar destruction with corresponding persistent anoxaemia of some portion of the venous blood. In each of these two conditions erythrocytosis may occur.

If present, its degree and variation serve to give some ideas as to the severity and progress of the lesion.

PRIMARY POLYCYTHAEMIA

(Polycythaemia Rubra Vera. Vaquez' Disease.)

In response to some unknown stimulus there is an excessive activity on the part of the erythropoietic tissues of the body. Destruction, of course, is necessarily correspondingly increased, otherwise the circulation would rapidly become impeded. But the resultant level at which the red cell count remains relatively stationary is raised, and, in progressive cases, is continuously though slowly increasing. The erythrocytes are larger rather than smaller than normal.

The Characteristic Pathological Findings are :

I. An Increased Red Blood-cell Count.
II. A Raised Haemoglobin Percentage.
III. A Slight Leucocytosis.
IV. The Viscosity of the Blood is increased.
V. The Urobilin Content of the Urine is frequently raised.

The red cell count is increased to any extent up to the level of about 12,000,000, according to the severity or chronicity of the disease. The cells are normal in appearance and shape, but an occasional normoblast is not uncommon. The haemoglobin is correspondingly increased, giving a colour index of near unity.

The variations in the blood-count give an accurate indication of the course of the disease.

There is generally a moderate leucocytosis to about the figure of 12,000, but this is by no means invariable.

The increase is largely a polymorphonuclear one.

Myelocytes in small numbers are not infrequent.

The viscosity of the whole blood, as measured by a haematocrit, is definitely increased.

Treatment

Two types of treatment need controlling by blood tests. *Phenylhydrazin* has been used with some success in treatment (5, 6), but its exhibition must be carefully controlled by simultaneous red and white cell counts and haemoglobin estimations. Indications for stopping the drug are a fall of the haemoglobin below 100 per cent. or a marked leucocytosis. A rise in the white count of more than 15,000 above its previous level indicates the necessity for withholding the drug temporarily. Some leucocytosis seems to be the usual precursor of the diminution in the red count.

A second form of treatment is a combination of *benzol with radium or X-ray therapy*. Alone these methods are somewhat disappointing, but in combination they seem to be in some cases very effective. Here again regular blood-counts should be the chief guide in determining the vigour or the continuance of treatment. Indications for stopping

the treatment are a fall in the haemoglobin percentage to below 100 and the appearance of a leucopenia. The usual leucocytosis can be allowed to disappear, but the count should not fall below 6,000.

LEUKAEMIA

Acute Lymphocytic Leukaemia.
Acute Myelocytic Leukaemia.
Chronic Lymphocytic Leukaemia.
Chronic Myelocytic Leukaemia.

General Considerations

In leukaemia, of whatever type, the dominating fact is that the normal formation of the white blood-cells is transformed into a foetal or primitive type. This change in kind is, as a rule, accompanied by a change in the amount of functioning white-cell-forming tissue. Normally this is confined, in the case of the granular cells, to the marrow of the bones laid down in membrane and to small areas in the marrow at the ends of the shafts of the long bones, and in the case of the lymphocytes probably also to these same areas to some extent and, in addition, to certain parts of the body rich in lymphatic tissues, the tonsils, the lymphatic tissues of the intestine, and the lymphatic glands.

The abnormal stimulus, whether inflammatory or neoplastic, present in leukaemia causes great hyperplasia in the normal leucoblastic areas, and also in those areas where such hyperplasia was present in the foetus or is ontogenetically possible.

Thus not only are the normal sites of white cell formation crowded with lymphoblasts or myeloblasts and similar abnormal tissue, but, in addition, the shafts of the long bones, the liver, and other organs of the body are similarly invaded.

Pathological Findings in Leukaemia

These events account for the pathological changes seen in leukaemia, which are:

I. Presence in the Blood of a Large Number of Immature White Cells.

II. An Over-crowding of the Bone-marrow resulting in :
   (*a*) Secondary Anaemia,
   (*b*) Thrombopenia late in the disease,
   (*c*) Diminution in the Number of Other White Cells in Lymphocytic Leukaemia.

III. Owing to the excessive fragility and therefore destruction of large numbers of immature white cells the urine contains an Excess of Uric Acid.

IV. Albuminuria is common, and is in many cases probably due to pressure upon the right renal vein as a result of excessive splenomegaly.

The **secondary anaemia** is in most cases of the chlorotic type, but terminally it may show reversion to the pernicious picture. Owing to the fact that the bone-marrow in lymphocytic leukaemia is replaced by a foreign structure (lymphoblastic tissue) its erythroblastic powers are progressively reduced and the anaemia becomes more marked with the progress of the disease. In myelocytic leukaemia, on the other hand, the normal functions of the marrow merely suffer the result of metaplasia, not of destruction and replacement; and the erythropoietic tissue, with the leucoblastic, tends to emit into the blood-stream a number of immature forms. Thus normoblasts and megaloblasts are common and have no especial significance, whereas in lymphocytic leukaemia they indicate severe marrow irritation and presumably destruction. It follows that a severe anaemia in myelocytic leukaemia is evidence of severity of the disease.

The **deficiency of platelets** tends to run parallel with the degree of anaemia; purpura and bleeding are common both in the terminal stages of chronic lymphatic leukaemia, and in the acute cases of either type. In the former case the deficiency is probably the result of replacement by lymphoblastic tissue of the platelet-forming cells of the bone-marrow, in the latter case it may be due to a toxic depression of the activation of those same structures. Terminally, especially in lymphatic leukaemia, the abnormal leucoblastic tissue seems to fail in its turn, with the result that the white cell count may fall to normal or even below, pro-

ducing the picture sometimes called **aleukaemic leukaemia.** The abnormal differential count in these cases persists.

Examination of case reports of so-called **aplastic anaemia** described in the literature reveals the fact that a number of them coincide in every respect, including the platelet deficiency, with the terminal hypoplastic stage in lymphatic leukaemia, with which indeed they may be identical.

In both types of leukaemia the picture, as regards the white cells, is typically dominated by the immature cells.

In lymphatic leukaemia this is due to a secondary aplasia affecting the granular cells, in myelocytic to the very large numbers of the abnormal elements. This is brought out by the fact that in the former disease a large diminution in the white count is accompanied by no proportionate increase in the percentage figures of the other cells, but often by an actual decrease, whereas in myelocytic leukaemia a return to a normal white count is accompanied by a return of the proportions of the various cells towards, if not to, normal.

ACUTE LYMPHOCYTIC LEUKAEMIA

So definite is the onset, and so brief the course of most cases of acute leukaemia, whether lymphocytic or myelocytic, that an acute infective process is often suggested. There is, however, no conclusive evidence of this.

The Pathological Findings in Acute Lymphatic Leukaemia are :

I. An Abnormally Large Number of Lymphocytes in the Blood, if the count is raised.

If the count is unchanged or diminished, the other constituents of the white blood count are even more diminished. In either case the percentage of lymphocytes is considerably raised, usually above 70 per cent. The other white cells do not show evidence of immaturity.

II. A Secondary Anaemia.

The lymphocytes are variable in size, shape, and staining reaction, many of them being immature. They are often

larger in the acute form than in the chronic, but this is not a fixed rule.

The actual white count tends to be less in acute than in chronic lymphatic leukaemia. Eosinophiles and basophiles are more reduced in number than are the polymorphonuclears, and these latter, together with the more numerous lymphocytes, comprise the majority of the white cells. The white count may be increased or decreased. Normal or subnormal white counts are most commonly found early or late in the disease or in the presence of septic complications. Typical differential white blood counts for each class are:

(1) **Acute lymphatic leukaemia (usual type), W.B.C. 35,000.**

Lymphocytes	31,200 per c.mm.
Polymorphonuclears	3,500 ,, ,,
Large mononuclears	240 ,, ,,
Eosinophiles	50 ,, ,,
Basophiles	10 ,, ,,

The lymphocytes were chiefly large lymphocytes, but varied considerably in size and in staining intensity.

(2) **Acute lymphatic leukaemia (aleukaemic type), W.B.C. 3,100.**

Lymphocytes	2,900 per c.mm.
Polymorphonuclears	200 ,, ,,
Eosinophiles	0 ,, ,,
Basophiles	0 ,, ,,

The red cell count shows, as a rule, a marked secondary anaemia. This is due to two causes, the marrow hypoplasia and the haemorrhages. At first chlorotic, it may terminally assume pernicious characteristics. An occasional myelocyte may be found, evidence of marrow irritation. The granular cells present are mature forms.

It should be remembered that chronic lymphatic leukaemia often ends with a picture identical with that of acute lymphatic leukaemia, and that acute lymphatic leukaemia may be simulated by acute myelocytic leukaemia.

ACUTE MYELOCYTIC LEUKAEMIA

This disease is analogous in most respects to acute lymphatic leukaemia, with the variation that myelocytes and myeloblasts take the place of lymphocytes in the blood

picture. The fact that myeloblasts are non-granular cells and stain, in the main, in a manner not dissimilar to that of large lymphocytes has led in the past to two mistakes.

When such cells comprised a large proportion of the white count the disease was wrongly diagnosed as acute lymphocytic leukaemia; when their proportion was rather less and when myelocytes were also present in fair numbers, the statement was made that acute mixed leukaemias occurred. The further observation was wrongly made that one type of leukaemia was not infrequently transformed into the other.

The correct explanation is to be found in the fact that an acute myelocytic leukaemia can be first observed at a stage when myelocytes comprise most of the abnormal cells. Later the myeloblastic tissues revert to a more and more primitive type, and send into the blood a less and less granular cell, eventually myeloblastic in morphology, and finally these non-granular primitive cells form the majority of the circulating leucocytes. Thus to a superficial observation the myelocytic picture has given place to a lymphocytic one.

By means of the oxydase stain these early myelocytes and myeloblasts can be shown to contain granules in some cases, differentiation thus becoming sometimes possible where the usual Romanowski stains fail.

The Chief Findings in Acute Myelocytic Leukaemia are :

I. Myelocytes and Myeloblasts in Numbers in the Blood-stream.

II. A Secondary Anaemia.

The myelocytes and myeloblasts occur in numbers and percentages similar to those of the lymphocytes in acute lymphatic leukaemia. An aleukaemic form of the disease is much rarer than in the lymphatic type.

The secondary anaemia is similar to that of acute lymphatic leukaemia, but nucleated red cells are rather more common.

CHRONIC LYMPHOCYTIC LEUKAEMIA

The Pathological Characteristics of chronic lymphatic leukaemia are:

I. An Increase in the Total Number of Lymphocytes in the Blood-stream, except in the Aleukaemic form of the disease, when they may be diminished. The percentage in all types is generally above 70.

II. A corresponding Diminution in the Granular Leucocytes, especially in the Aleukaemic form.

III. A Secondary Anaemia, generally proportional in severity to the stage of the disease.

IV. A Diminution in the Platelet Count, most marked in the terminal stage.

The lymphocytes in chronic lymphatic leukaemia are most commonly of the small variety. They may show abnormalities in staining, ghost forms being not uncommon. The leucocyte count is less as a rule than is that of myelocytic leukaemia, the figure being generally below 100,000. Rarely figures up to 1,000,000 are met with.

The secondary anaemia is more marked in chronic lymphatic than in chronic myelocytic leukaemia. **Vincent's angina** is a common secondary infection during the course of all types of leukaemia. The picture and characteristics of acute lymphocytic leukaemia often supervene terminally.

Diagnosis

A number of diseases are accompanied by a lymphocytosis in the blood. Some of them are liable to be mistaken for lymphatic leukaemia, others are sufficiently distinctive to prevent the mistake from being made. They are pertussis, rubella, infective mononucleosis or glandular fever, mumps, some cases of streptococcal tonsillitis in children, and Vincent's angina. A point that is of some diagnostic value in these cases, and one that should always be investigated, is the type of lymphocyte present. It is generally the normal small lymphocyte of the blood, immature forms being absent. In lymphatic leukaemia, on the other hand, the cells may vary in size and staining properties.

Pertussis, especially if complicated by broncho-pneumonia, is sometimes accompanied by a very large lymphocytosis. The writer has observed a count of 176,000, of which lymphocytes formed the larger proportion.

The two points in the blood-count of such cases worthy of note are: (1) The other cells are generally all increased. If percentages and not absolute figures are reckoned this increase will probably become a percentage decrease and will be missed. (2) There is no accompanying secondary anaemia, or only one of slight degree.

Rubella in the absence of a rash may well simulate lymphatic leukaemia in a child. The spleen is often palpable, the superficial lymphatic glands show general enlargement, and there is an actual lymphocytosis, sometimes to a considerable degree.

The lack of diminution in the numbers of the remaining white constituents of the blood and the absence of a secondary anaemia may be suggestive, the opposite findings being characteristic of leukaemia. In some cases a second complete examination after an interval of a few weeks may be necessary to decide the point. In rubella the change will be towards normal figures.

Infective mononucleosis or glandular fever is a disease of childhood characterized by fever, glandular enlargement, secondary anaemia, and a lymphocytosis.

The same criteria are used as in rubella to eliminate lymphatic leukaemia.

Mumps may be accompanied by a lymphocytosis, but the clinical condition is generally distinctive.

Streptococcal tonsillitis and Vincent's angina. These two conditions may produce a picture having quite a close resemblance to lymphatic leukaemia, especially in children.

In either case the infection may occasionally cause a lymphocytic rather than the usual polymorphonuclear reaction. The similarity is still further increased by the two facts that Vincent's angina is a common concomitant of true leukaemia, and that a sore throat is not infrequently among the early symptoms of the major disease.

In a few rare cases the favourable outcome has been the

only proof that leukaemia was not present, so close may the resemblance be in all respects.

Points against leukaemia are those mentioned above in correlation with rubella.

Prognosis

The ultimate prognosis is invariably fatal, but some information can be gathered from the red cell, white cell, and platelet count as regards immediate prognosis. The central fact of importance is the regenerative power of the bone-marrow. Deficiency of this as shown by a falling red cell count or by an aleukaemic white count (not produced by treatment) is of serious import. The degree of the leucocytosis gives no help in prognosis; high figures in themselves are insignificant.

CHRONIC MYELOCYTIC LEUKAEMIA

The Pathological Findings in chronic myelocytic leukaemia are:

I. The Presence of many Myelocytes, and other Immature White Cells, of all three varieties, in the Bloodstream.

II. A slight Secondary Anaemia in the later stages.

The white cell count is higher than that characteristic of lymphatic leukaemia, a figure of above 500,000 being common. This is made up of granular white cells of all three varieties and their corresponding myelocytes.

Acute infective complications, such as pneumonia, not infrequently reduce the white count and even the blood picture to normal. But this phase is transient and is terminated with the intercurrent disease, the original myelocytic count supervening. Contrary to what is true of lymphatic leukaemia, all the white cells show an actual increase in figures, the lymphocytes being included. In most cases the most numerous cell is the polymorphonuclear; this is closely followed by the neutrophile myelocyte. Eosinophiles and basophiles and their corresponding myelocytes are also present in large numbers. In no other

disease do these latter two types of myelocytes appear in the blood-stream, and their definite presence even in very small numbers is almost conclusive evidence in a suspected or early case. Basophiles are generally present in definitely raised numbers. When remissions occur as a result of treatment the increase often persists.

The writer has seen a case where splenomegaly was associated with the presence of a few neutrophile myelocytes in the blood-stream but with a basophile count about three times the normal figure, the total leucocyte count being about 12,000. Time showed that this was a very early case of chronic myelocytic leukaemia.

Prognosis

As in lymphatic leukaemia the essential factor to be determined is the reacting power of the bone-marrow. This is mirrored most closely in the red cell and platelet counts.

Blood Changes occurring during the Treatment of Leukaemia

Both types of chronic leukaemia can be effectively treated, so far as symptoms are concerned, by benzol or by the use of radium or X-ray radiation. As might be expected these agents, which in sufficient dosage produce hypoplastic bone-marrow changes, are usually more effective in chronic myelocytic rather than in chronic lymphocytic leukaemia.

X-ray and Radium Treatment. Regularly spaced doses should be given at weekly intervals and close watch should be kept upon the red cell and leucocyte counts. The usual early result of treatment is to reduce the white count and to leave the red cell count unaffected, or indeed the latter may actually be increased.

Continuance of dosage is determined by two factors, the degree and rate of diminution in the white count and the change in the red cell count. If the fall in the white count is very rapid a dose should be omitted; if the red cells begin to diminish at all in number dosage should be stopped.

The figure to which it should be the aim to reduce the

white count is 12,000–15,000. After this point has been reached, it will probably be found that the diminution will go on spontaneously to the level of about 8,000. A fall will almost always continue for 10–14 days after the last dose of X-rays. Individuals vary greatly in their sensitivity to X-rays, and the first dose should always be small (about $2\frac{1}{2}$ H., or half a pastille dose, to the spleen) and the reaction of the blood picture carefully watched. Sometimes a single dose will reduce a white count of 500,000 by half within ten days.

Benzol dosage is guided in a similar manner by the rate of fall in the white cell count and by the first appearance of a diminution in the erythrocyte figure.

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C. DISEASES OF THE CARDIOVASCULAR SYSTEM

X. DISEASES OF THE HEART AND PERICARDIUM.

Pericarditis—

- Acute Rheumatic Pericarditis.
- Scarlatinal Pericarditis.
- Septic Pericarditis.
- Tuberculous Pericarditis.
- Uraemic Pericarditis.
- Pericardial Transudates.

Myocarditis—

- Rheumatic Carditis.
- The Thyrotoxic Heart.
- Syphilitic Myocarditis.
- Myocardial Failure.
- Cardiac Infarction.

CHAPTER X

DISEASES OF THE HEART AND PERICARDIUM

PERICARDITIS

ACUTE RHEUMATIC PERICARDITIS

Some minor and localized lesions of the pericardium occur in many cases of acute rheumatic cardiac infection. The abrupt generalized lesion of the pericardium, which produces the symptoms and signs known by the name of acute rheumatic pericarditis, is less common.

The Clinical Pathological Findings are:

I. Leucocytosis.
II. Anaemia.
III. Abnormalities of the Pericardial Fluid.
IV. Abnormalities of the Pleural Fluid.

Leucocytosis is almost invariably present in a degree higher than that normally accompanying an active rheumatic carditis. The figure is generally above 12,000, and may be as high as 25,000. A sudden increase in the leucocyte count in a rheumatic patient when accompanied by a corresponding increase in the degree of pyrexia is suggestive of the development of a pericarditis.

Anaemia. Simultaneously with the above change a rapid anaemia, of the chlorotic type, develops. The haemoglobin frequently falls to 50 per cent. or less. A dying down of the pericardial inflammation is followed by a diminution in this anaemia.

The pericardial fluid in rheumatic pericarditis has the following characteristics:

It is yellowish, or any shade from this to red, according to the degree of admixture with blood. A clot forms on standing. The specific gravity in the oxalated specimen is above 1,015, and the albumin content over 3 per cent. The cells present are chiefly, sometimes entirely, polymorphonuclear leucocytes; a few lymphocytes and endothelial cells may be present. It is almost always sterile on

culture, though a few cases are on record from which a streptococcus has been grown. There is, however, no convincing evidence that a streptococcus is the cause of the disease.

A left-sided **pleural effusion** having characteristics identical with those present in the pericardial fluid occurs in most cases of rheumatic pericarditis. Owing to its greater accessibility it is of considerable diagnostic value.

SCARLATINAL PERICARDITIS

is of two varieties: that which accompanies other septicaemic streptococcal complications during the disease, and that which follows later in its course or during convalescence.

The former has the characteristics of any other 'septic' pericarditis (see below), and the latter is probably identical with rheumatic pericarditis.

SEPTIC PERICARDITIS

Pericarditis may be due to any pyogenic organism. The commoner associated varieties are streptococci, staphylococci, pneumococci, gonococci, *Bacillus coli communis*, and *B. typhosus*. The condition arises as a terminal infection or as a metastatic septicaemic phenomenon.

Pathological Findings

I. Leucocytosis.
II. Anaemia.
III. Abnormalities of the Pericardial Fluid.

The **polymorphonuclear leucocytosis** is considerable, and except in fulminating cases is invariable.

The **anaemia** is as a rule progressive if the patient survives for any length of time. In the pneumococcal cases, where drainage has been successfully carried out, a diminution in the degree of anaemia is an indication of improvement.

The **pericardial fluid** has the following characteristics: It is opaque, yellowish, greenish, or reddish in appearance, according to the type of organism concerned and the

amount of bleeding that may have occurred; it contains more than 3 per cent. of albumin, and is highly purulent.

The cells present are polymorphonuclear leucocytes in great predominance.

The organism is present in films and frequently also on culture.

TUBERCULOUS PERICARDITIS

The findings in tuberculous pericarditis are analogous in all respects to those of tuberculous pleural effusion (see p. 260).

URAEMIC PERICARDITIS

Pericarditis is a moderately frequent terminal finding in cases of chronic nephritis suffering from uraemia. It is of two natures, sterile or infective. In the latter case the organism varies considerably; pneumococci, streptococci, staphylococci, *B. coli* have all been described.

In both cases it generally accompanies a very much raised blood urea, the average figure (1) being about 260 milligrams per 100 c.cm., a severe secondary anaemia of about 48 per cent. haemoglobin and 2,700,000 red blood-cells per c.mm., and a moderate leucocytosis, about 15,000.

Prognosis. The infected cases are rapidly fatal, but the others may continue for a few months, though the average length of life is 2–3 weeks.

PERICARDIAL TRANSUDATES

In renal and chronic cardiac disease and in certain other cachectic states a curious type of pericardial effusion sometimes occurs (2). Its characteristics are not analogous to transudates in other positions. The fluid is alkaline, usually clear, and either colourless or of a yellow or green tint, but may be turbid from degenerate endothelial cells and even tinted by bile or blood. It may clot on standing and have an albumin content of over 3 per cent. in contradistinction to transudates elsewhere.

The pericardial effusions found in **new growth** and **lymphadenoma** are similar to those present in the pleura.

MYOCARDITIS

RHEUMATIC CARDITIS

There are two pathological investigations of value in the diagnosis and treatment of active rheumatic infection of the heart. They are the presence of a leucocytosis and of a secondary chlorotic anaemia. Infection of the myocardium and of the endocardium is simultaneous, to some degree, in all cases, and it is probable that the widespread myocardial lesion is more important from this point of view than are the comparatively isolated and localized foci in the substance of the valve.

Leucocytosis of a mild degree, as Swift has shown, is present in most cases in the active stages of inflammation, and may continue after the pyrexia has disappeared. It is a phenomenon of great value in judging the presence of activity. A persisting leucocytosis, even when the increase above normal figures is only one of 3,000, is a definite indication that the patient should be kept at rest in bed. The leucocytosis is polymorphonuclear in type. A sudden considerable increase in it accompanies the onset of an acute pericarditis.

A **secondary anaemia** of some degree is present in most cases of active carditis. Its extent is roughly proportional to the severity of the lesion. An increase in it suggests an accentuation and a diminution an amelioration in the infective condition.

The blood culture in acute rheumatism is sterile. Recent work at the Rockefeller Institute has corroborated the fact that the disease cannot be ascribed to any definite causative organism. The existence of a problematical *Streptococcus rheumaticus* is still a matter of conjecture.

THE THYROTOXIC HEART

In typical exophthalmic goitre the myocardium may suffer severely from the effects of thyroid hypersecretion. The basal metabolic rate will here give valuable help as to the course of the disease (see p. 335). It not infrequently happens, however, that the presence of a small or

substernal thyroid adenoma is the cause of severe heart failure, frequently with auricular fibrillation, in women of middle age (3). The cardiac symptoms are here so well marked that attention may be focused upon them, the causative lesion remaining unnoticed. In such patients a determination of the basal metabolic rate, allowance being made for the increase due to dyspnoea, which is generally less than 125 per cent., may be of valuable service in pointing to the true cause of the condition. Other symptoms of hyperthyroidism are usually present, though exophthalmos may be absent. In calculating the basal metabolism of such patients, allowance must be made for the increase of weight due to oedema. Myxoedema with a low basal rate may also cause heart failure.

SYPHILITIC MYOCARDITIS

Syphilis can affect the heart either through disease of the coronary vessels, or by the formation of gummata, or possibly by a more acute and diffuse primary myocarditis. The only pathological investigation that is likely to yield information of value is the Wassermann reaction.

Longcope summarizes the statistical position as follows: In general syphilitic vascular disease the Wassermann reaction of the blood is positive in 25–68 per cent., in aortic valvular disease in 75–80 per cent., in aneurysm of the aorta in 85–95 per cent., and in aortic disease in general in 75–88 per cent.

Stokes (4) believes that by use of the more delicate Kolmer technique or by employment of a provocative injection of an arsenical compound, these percentage figures can be increased. The justifiability of the latter procedure, in view of the danger of a local Herxheimer reaction, is open to question except in carefully selected cases.

MYOCARDIAL FAILURE

In all cases of heart failure, acute or chronic, an infective cause or accessory factor should always be eliminated. The causes of acute failure are nearly always infections, the commonest being acute rheumatism, scarlet fever, diphtheria, influenza, and tonsillitis. Chronic failure is frequently

accentuated and even caused by infections of the nasal sinuses, tonsils, bronchi, lungs, or urinary tract.

A case of auricular fibrillation, particularly if belonging to the rheumatic type, which does not readily respond to digitalis treatment must be presumed to be suffering from a secondary infection unless the contrary can be proved.

CARDIAC INFARCTION

Of recent years the clinical signs of cardiac infarction have been the subject of careful study. In addition to the typical pain, the raised rectal temperature, the collapse, the electrocardiographic changes, and the later pericarditis, a valuable clue is present, in many cases, in the presence of a **leucocytosis**. Libman (5) says, 'We have come to believe that no other finding is of greater diagnostic value. It is even safe to say that it is the most frequently significant feature of thrombosis of the coronary arteries'. The leucocytosis is polymorphonuclear in type; it appears within a few hours of the onset, and its subsequent variation is of some definite value in prognosis. Should it disappear within a day or two it is to be presumed that progressive necrosis of the heart-muscle is not occurring. But should it persist, especially if associated with a pericardial rub, a grave prognosis is suggested. The count is usually of the degree of about 17,000, but may reach 25,000. Absence of a leucocytosis within the first few days of the onset of symptoms suggesting a coronary thrombosis reduces the likelihood of the presence of the condition.

Other conditions producing a sudden left-sided pain together with fever and leucocytosis should be borne in mind. Such are pulmonary infarction, pleurisy, and splenic infarction.

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D. DISEASES OF THE GASTRO-INTESTINAL SYSTEM

XI. DISEASES OF THE STOMACH

The Examination of Stomach Contents.
The Presence of Occult Blood in the Stools.
Pathological Findings in Diseases of the Stomach and Duodenum.

XII. EXAMINATION OF THE STOOLS

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Microscopical Appearance.
Intestinal Animal Parasites.
Bacteriology.

XIII. DISEASES OF THE INTESTINES IN ADULTS

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Putrefactive Intestinal Indigestion.
Tuberculous Enteritis.
Sprue.
Appendicitis.
Amoebic Dysentery.
Bacillary Dysentery.
Mucous Colitis.
Chronic Ulcerative Colitis.
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Intoxication.
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- The Glycuronic Reaction.

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- Obstructive.
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- Haemolytic.

The van den Bergh Test.
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Spirochaetosis Ictero-haemorrhagica.
Acute Yellow Atrophy.
Acholuric Familial Jaundice.
Cirrhosis.
Syphilis.
Hydatid Disease.
Malignant Growths.
Suppurative Pylephlebitis.
Gall-stones.
Acute Cholecystitis.

XVII. DISEASES OF THE PERITONEUM.

Peritonitis.
Ascites.

CHAPTER XI

DISEASES OF THE STOMACH

THE EXAMINATION OF STOMACH CONTENTS

The Resting Fluid and the 'One-Hour Meal'

With Ryle's modification of the Rehfuss stomach-tube (see Appendix, p. 369) the fluid present in the stomach after a night's fast is easily obtained. Normally, the amount of this fluid is less than 50 c.cm.; a larger quantity indicates delayed emptying or hypersecretion. Bennett recommends that the patient be given a glass of milk and a charcoal biscuit on the evening before the test; the presence of charcoal in the resting fluid is evidence of pyloric obstruction. The presence of blood and of lactic acid is also investigated; the significance of these findings is discussed later.

When the resting fluid has been removed, the patient drinks one pint of oatmeal gruel, or the meal recommended by MacLean (1) (for the preparation of which see Appendix, p. 370). After one hour the stomach contents are withdrawn and are examined:

1. For the presence and amount of free hydrochloric acid.
2. For lactic acid, if hydrochloric acid is absent.
3. For blood, bile, and mucus.

The Fractional Test Meal.

For this investigation the procedure described above is adopted, but specimens, each of about 10 c.cm., are withdrawn at intervals of a quarter of an hour for two to two and a half hours, the final specimen consisting of all that remains at this time. In this way one can follow the changing conditions throughout gastric digestion.

The amount of free hydrochloric acid in the resting fluid is usually very small. In the first fraction the percentage of free HCl varies, according to Bennett and Ryle, from zero to 0·085. Successive samples show an increasing hydrochloric acid concentration until a maximum is reached after an interval which is very variable, but usually from one

to one and a half hours. The height reached also varies considerably, but is commonly in the region of 0·16 per cent. The concentration then falls, slowly or rapidly. **The general form of the curve is of more importance than the actual figures.**

It is known that the fall in free hydrochloric acid in the later samples is due to regurgitation of alkaline duodenal contents, and not to diminished secretion. Such regurgitation being a normal process, it follows that the percentages of free HCl found in successive samples give no indication of the amount of gastric secretion; this is given only by estimation of the total chloride content of each sample.

We may now consider the effect on the hydrochloric acid curve of certain abnormalities of stomach function. If regurgitation of duodenal contents does not take place, a condition which obtains in spasm of the pylorus from various causes, the result is a curve of the hypersecretory type; the concentration of HCl rises to an unusually high level. It may continue to rise in each successive sample, being highest in the last; Bennett and Ryle (2) call this the 'climbing curve'. It is important to realize that these curves indicate not excessive secretion of acid, but absence of the normal duodenal regurgitation, from spasm of the pylorus. As we have seen, actual hypersecretion is only demonstrable by an estimation of total chlorides.

It may be appropriate to point out here that spasm of the pylorus, though most often due to pyloric or duodenal ulcer, may also occur in the absence of organic disease of the stomach and duodenum, as a reflex phenomenon.

Excessive regurgitation of duodenal contents results in a curve of the 'hyposecretory' type, and it is scarcely necessary to add that these curves do not indicate diminished gastric secretion. The term 'achylia gastrica' is applied to designate those cases where no free hydrochloric acid is found in any fraction, irrespective of the cause of this. As judged by the total chloride curve, actual absence of gastric secretion is very rare (3).

In each fraction the percentage of 'total acid' is esti-

mated. This represents free hydrochloric acid, together with hydrochloric acid combined with protein, and, under pathological conditions, organic acids, chief of which is lactic acid. Under normal conditions the 'total acid' curve follows the free HCl curve in general form, at a slightly higher level.

Each fraction is also examined for starch, bile, and macroscopic blood. Starch will be present in each fraction as long

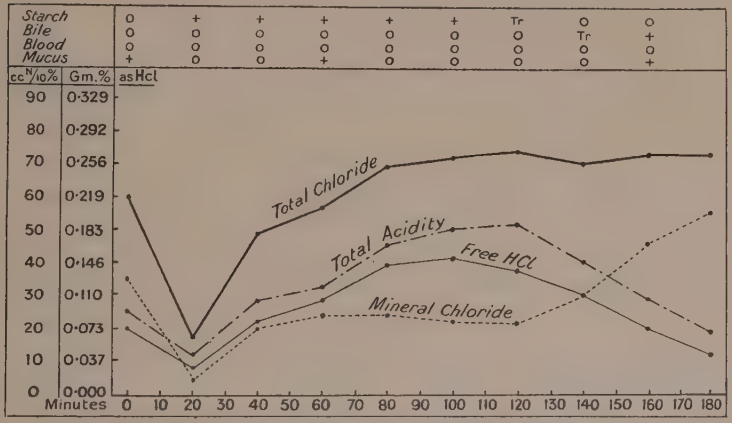


Fig. 2. Fractional test meal: normal curves.

as any of the meal remains in the stomach; the point at which it disappears therefore gives a measure of the rate of emptying of the stomach. By examining the fraction for bile, confirmatory evidence is obtained as to normal regurgitation of duodenal contents.

THE PRACTICAL VALUE OF EXAMINATION OF THE STOMACH CONTENTS, WITH CHOICE OF METHOD

Delayed Emptying

Any gross delay in emptying, such as occurs in mechanical obstruction to the pylorus, is revealed by the amount and character of the resting fluid. Fuller information as to rate of emptying is obtained by the fractional test meal, for we are given the additional facts of the time of disappearance of starch, and the amount of the final specimen.

Carcinoma of the Stomach

The presence of an excessive amount of resting fluid, containing altered blood and lactic acid, is suggestive of carcinoma. In this condition specimens removed after a test meal very commonly show absence of free hydrochloric acid, together with the presence of definite amounts of lactic acid. The information is given by the one-hour meal, and it is of no advantage to use the fractional method.

Pyloric and Duodenal Ulcer

The fractional test meal gives information as to excessive irritability of the pylorus, but no certain information as to the presence or absence of organic disease in this region. The 'climbing type' of hydrochloric acid curve is probably most often caused by an ulcer in the region of the pylorus, but there are other causes. Pyloric spasm, as we have seen, is responsible for this type of curve, and it may be a reflex phenomenon occurring in the absence of organic disease of the stomach. In most instances examination of stomach contents is of little help in deciding whether peptic ulcer is present or not.

Pernicious Anaemia

The complete absence of free hydrochloric acid throughout the whole course of digestion is an important observation in considering the diagnosis of a doubtful case of pernicious anaemia (see p. 123). For this information, of course, the fractional method is needed.

Thus in practice, examination of stomach contents is of little help in the diagnosis of most cases presenting symptoms of digestive disorder. The one type of case in which the examination ought always to be carried out is that in which the general features suggest the possibility of carcinoma of the stomach; the 'one-hour meal' method is adequate for this purpose.

EXAMINATION OF THE FAECES FOR OCCULT BLOOD

A peptic ulcer is almost always associated with the presence of blood in the faeces; so also is carcinoma of the

stomach. The blood is usually in small amount only, and is intimately mixed with the faeces, and is recognizable, therefore, only by chemical tests. It is thus of great value to test the faeces for occult blood in all doubtful cases of organic disease of the stomach or duodenum.

A. G. Ogilvie (4) has investigated the alleged fallacies in connexion with the test for occult blood, and particularly the influence of diet. He recommends Gregerson's method of carrying out the benzidin test, and considers this preferable to the pyramidon test, as it is less delicate and therefore less liable to fallacy. This test is one which the practitioner can easily carry out for himself; the details are given in the Appendix (see p. 371). Among Ogilvie's conclusions are firstly that meat, and especially underdone meat, may cause a green coloration after thirty seconds with Gregerson's test, and a positive result with the pyramidon test; further, that a blue or blue-green colour with Gregerson's test obtained within thirty seconds is proof of occult blood in the stools, irrespective of the patient's diet. Marked gum bleeding, haemoptysis, or bleeding haemorrhoids, must be excluded before the origin of this blood may safely be ascribed to the alimentary tract. Iron medicines produce no occult blood reaction in the faeces, but the ingestion of red bone-marrow may do so.

Thus, in practice, probably no precautions as regards diet are necessary if Gregerson's test is used. The significance, however, of a positive result is so important that it may be wise to eliminate meat for three days before applying the test. No other article of diet need be excluded.

MacLean points out that the special diet usually ordered often results in cessation of the bleeding.

PATHOLOGICAL FINDINGS IN DISEASES OF THE STOMACH AND DUODENUM

Carcinoma of the Stomach

The Blood. Anaemia, usually of the chlorotic type, develops in all cases. Early in the disease the red cell count may be normal or but slightly diminished. Simon puts the

average figure at 4,000,000. The colour index is low in the majority of cases. Exceptionally, a marked loss of red cells develops early in the disease, the colour index remaining normal or being actually increased; the blood picture then resembles that of pernicious anaemia.

The leucocytes may be normal or slightly increased.

The Stomach Contents. The importance of the examination of stomach contents in cases where there is a suspicion of gastric carcinoma has already been sufficiently emphasized. Free hydrochloric acid is absent in the majority of cases, and in these lactic acid is present. The occurrence of this combination is highly suggestive, and alone constitutes sufficient grounds for an exploratory laparotomy. In other conditions associated with absence of free hydrochloric acid, such as chronic gastritis and pernicious anaemia, lactic acid is generally not found. Lactic acid may be found in the stomach contents in the very early stages of a carcinoma of the stomach, before any obstruction has developed. The presence of free hydrochloric acid must not be taken as excluding cancer.

The Stools. Occult blood is found in practically every case, and its absence would point definitely against carcinoma.

Gastric Ulcer

The Blood. Many long-standing cases develop a moderate degree of anaemia, in which a low colour index is the rule. Severe haemorrhages may of course lead to very marked anaemia.

The Stomach Contents. The results of a fractional test meal may show nothing abnormal in the acid curves. In many cases of pyloric ulcer 'hypersecretory' curves are obtained, and there may be evidence of delayed emptying. Blood is frequently present, in small amounts.

The Stools. Occult blood will be found in the great majority of cases.

Duodenal Ulcer

The Blood. As in gastric ulcer, anaemia may develop.

The Stomach Contents. There is usually a marked in-

crease in the percentage of free hydrochloric acid; often a curve of the 'climbing' type is obtained.

The Stools. Occult blood is present in the large majority of cases.

Chronic Gastritis

The Blood. There is no change in the blood except in cases of long standing, when some slight diminution in the haemoglobin percentage may be found.

The Stomach Contents. The most characteristic change is an excess of mucus in the contents removed after a test meal. A free hydrochloric acid curve of the hyposecretory type is usually obtained, and free hydrochloric acid is commonly absent. If the stomach is washed out, and a test meal given, no lactic acid is found in the contents removed after one hour.

CHAPTER XII

EXAMINATION OF THE STOOLS

GENERAL APPEARANCE

Amount and Number. The normal average quantity of the moist stools is about seven ounces per diem. Their quantity varies greatly in different individuals and from day to day. They are composed of water, bacteria living and dead, undigestible and undigested debris, intestinal secretions and excretions, and cells. Of these constituents the water probably varies most in amount when the diet remains fairly constant. Vegetables and starchy foods increase and animal proteins decrease the bulk of the motion.

Gastric disorders have little effect upon bulk, but failure of intestinal digestion or secretion, whether the cause be primary, or secondary as in liver and pancreatic disease, has a pronounced effect in increasing the quantity. This increase is due to two factors: a diminution in the quantity of food absorbed and an increase in the bacterial activity.

Besides varying with the amount per unit of food taken, the faecal quantity depends temporarily in some cases upon retention. Large quantities are passed if the colon be artificially emptied after a period of partial obstruction, as in Hirschsprung's disease and in chronic constipation.

CONSTIPATION AND DIARRHOEA

Constipation can be defined as a condition where the stools are fewer in number and in amount, and diarrhoea as the converse of this.

Constipation is due to lack of residue, as occurs in vomiting and starvation, in pyloric stenosis, or upon an easily assimilable diet; or it results from lack of evacuating power consequent upon atony of the lower bowel or obstruction of it.

Two macroscopic observations are worthy of mention with regard to constipation: the speed of transit of the food

through the intestinal canal, and the presence or absence of an associated mucous colitis.

The first can be determined by giving ten grains of carmine in a capsule after breakfast and by observing the time taken for the colour to appear in the stools. It should be remembered that the passage of motions can be regular in the presence of a definite delay, there being a considerable accumulation in the colon. The normal transit time through the intestinal canal is the period 24–72 hours after ingestion of the dye. The colour begins to show in the motion at about the former and vanishes at about the latter time. The second factor, that of mucous colitis, is proved present by the finding of ropy flakes of mucus admixed with the stools.

Diarrhoea may be present as an acute or as a chronic phenomenon. In the former case it may be due either to irritative or to nervous causes, in the latter case the cause is generally irritative.

Shape

The shape of the motions depends largely upon their consistency, which in turn varies with the water content. A meat diet tends to produce firm, discrete, smallish motions, and a vegetable diet softer, less formed, excreta. The diameter depends largely upon the tone and size of the anal orifice, ribbon-like stools being often the result of rectal stenosis or spasm. Organic stricture of the lower bowel gives rise more often to a stool of mixed consistency in which harder pencil-like lengths are present.

In constipation the faeces tend to form rounded balls which are more separate and harder according to the degree of water absorption.

Colour

The normal colour is yellowish or brown and is due to the presence of stercobilin. Generally a lighter colour is present when the bowels are moving freely. Exposure to the air tends to make the surface darker than the interior.

Pale, colourless, watery motions are present in cholera,

where they are almost entirely the result of the excessive secretion from the inflamed mucosa.

Pale, firm motions are present when there is obstruction to the common bile duct.

Pale, pultaceous motions are seen in some cases of pancreatic insufficiency, in sprue, and in tuberculous peritonitis; here the colour and the generally coexistent foetor are due to the non-absorption of fat. In sprue they are often also frothy.

Black or dark-coloured excreta follow the ingestion of iron, manganese, and bismuth, or the presence of blood in the gut for a sufficient period. A dark tint is also produced by red wine and by some fruits, and a grey one by chocolate and cocoa. An unusually **yellow** tint follows the ingestion of santonin, rhubarb and senna, and sometimes also the too rapid transit of the intestinal contents. In the former case the colour is due to chrysophanic acid, and in the latter case to the presence of unaltered bile pigment.

Green stools are common in children and infants (p. 205) with diarrhoea, and sometimes occur in adults, the colour being due to biliverdin. Green stools may be present in typhoid fever if the large bowel is ulcerated. *B. pyocyaneus* may occasionally be the cause of green coloration.

A **red** colour is present when bleeding occurs into the large bowel or rectum, and has also been ascribed in certain rare cases to the activity of *B. prodigiosus*.

Odour

The normal odour of the faeces is due to the presence of indol and skatol; changes in it are produced by abnormal bacterial fermentation.

In acute enteritis the earlier stools are often offensive, while the later ones become nearly odourless, the time for putrefaction being reduced.

In chronic pancreatitis a curiously unpleasant smell, like that of rancid bacon, is sometimes noticeable. The same odour is often present in coeliac disease in children.

When severe destruction of tissue occurs, a gangrenous odour may be present. Examples of this may be found in

severe acute dysentery, either amoebic or bacillary, carcinoma of the lower bowel, and gangrenous pancreatitis.

Reaction. Normal stools are nearly neutral in reaction. In fermentative conditions they are acid, and in putrefactive alkaline.

MACROSCOPICAL FAECAL CONTENTS

Certain definite macroscopical objects are not infrequently present. The commoner examples are:

Indigestible Objects in the Food.
Mucus.
Casts.
Blood.
Pus.
Tissue Masses.
Gall-stones.
Enteroliths and Coproliths.
Parasites.

Indigestible Objects. In children large fragments of food are not infrequently passed almost unchanged, particularly in the presence of diarrhoea. Examples are: gooseberry skins, pieces of potato, banana, and apple; their recognition is generally easy.

Apart from these, more minute pieces of undigested material suggest a definite defect in splitting or absorption.

Connective Tissue Fibres may appear in small numbers in normal stools; in large numbers they are evidence of deficient gastric digestion. They may be mistaken for pieces of mucus, but are of more fibrillar shape, of firmer consistency, and of a yellow-white colour. Microscopic examination will prove their nature.

Elastic tissue is of no significance. It can be distinguished by its clean white colour.

The presence of masses of **undigested meat** may be due to diarrhoea or to deficient function of pancreatic or intestinal ferments, and cannot be made accountable to either one of these factors in particular. A pancreatic lesion is the commonest cause (see p. 212).

Fats may be present occasionally in an undigested form in the stools in severe disease of the pancreas (see p. 211). In sprue the excess is due, as in coeliac disease, to deficient absorption.

The greatest part of the **mucus** found in faeces originates from the goblet cells of the large intestine, a smaller fraction from those of the small gut, and a fraction probably from the bile. The latter two sources are normally eliminated by the digestive action of the lower intestine, so that the presence of mucus in any quantity indicates a lesion of the colon, sigmoid flexure, or rectum. On the other hand, the absence of mucus does not exclude a catarrhal lesion of the upper intestine. Mucus in quantity is an expression of intestinal irritation or inflammation. In small amounts it is a normal finding.

The colour and appearance of the mucous masses may be of significance.

The more inflammation there is present the more opaque will be the mass from contained cells and cellular debris. A yellowish green colour suggests a high origin (the result of bile staining). The faecal pigments sometimes stain it brownish. Mucus must be distinguished from connective tissue, from cellular fragments from the intestinal wall, and from vegetable matter. Chemical and microscopical tests are adequate.

The more intimate the mixture of mucus with faeces the higher up as a rule is the lesion. In diseased conditions of the descending colon, sigmoid, and rectum, the mucus may be separated from the rest of the stool.

Casts

Casts of the gut are generally composed of mucus, but occasionally they may be 'diphtheritic' in character. The former are found in acute and chronic inflammations of the large bowel. From an examination of their cellular content some evidence can be obtained as to the presence or severity of an underlying inflammation. Mild irritation produces no cellular exfoliation, and the severity of an inflammation is as a rule proportional to the number of cells present.

Further evidence as to the acuteness of an inflammation can be obtained from the type of cell, red blood-cells and polymorphonuclears indicating an acute, and epithelial cells alone a more chronic process.

Diphtheritic casts are occasionally present in diphtheria and in severe dysentery. In either case they indicate a bad prognosis when associated with haemorrhage.

Blood

The colour of blood-containing stools varies from red, if the bleeding has occurred within a short time of the evacuation, to black, where a long period intervenes. Thus, in order to deduce the probable site of haemorrhage from the colour of the stools, the chief factor to be considered is the presence of diarrhoea or of constipation. Occasionally a profuse duodenal haemorrhage may stimulate a bowel movement, some of the recently shed blood escaping; in this case the motion will be red.

The viscid tarry stools of 'diarrhoea melaena' are characteristic, and can only be confused with those coloured by charcoal or by certain fruits. The more intimate the admixture of blood the higher as a rule is its source. The larger the quantity the more likely is the origin to be gastric or duodenal. On the other hand, the smaller, redder, and more separated the blood, the more probably does it come from the large intestine.

The presence of admixed mucus in any quantity strongly suggests a colonic origin.

Traces or flecks of blood on the surface of the motion suggest haemorrhoids. Red blood is also present in papilloma, polypus, anal fistula, and bilharziasis.

The stools, when digestion is normal, and in the absence of a meat diet, do not give a positive reaction to the chemical tests for occult blood. A positive reaction therefore indicates a bleeding-point somewhere from the posterior nares and teeth to the anus (p. 164).

Pus

This as a rule is not manifest to the naked eye; occasionally, however, the rupture of an abscess from the region

of the appendix, the gall-bladder, the kidney, the psoas muscle, or from the perigastric area produces visible pus in the stool. The nearer to the anal orifice the less will be the admixture with the motion, and as a rule the greater will be the visible quantity of pus.

Tissue Fragments

Tissue fragments may arise from sloughs of dysenteric and other ulcers, from portions of sloughed intestine in intussusception, and from growths, polypoid, innocent, or malignant.

As a rule, microscopical examination will be of considerable aid in diagnosis, though occasionally destruction of the tissue has gone so far as to make this uncertain.

Gall-stones

In cases suspected of cholelithiasis an examination of the stool day by day by a process of fragmentation, washing, and sifting will frequently show the presence of gall-stones. The unpleasantness and tedium of the process is its only handicap. Some form of electrically driven cylindrical sieve fitted with a water-supply would remove the difficulty. The finding of a faceted stone indicates that it was one of several. The presence of a large gall-stone suggests the presence of a fistula connecting the bile passages with the intestine, probably the colon, passage through the common duct having been impossible.

Other bodies simulating gall-stones are: calcified vegetable matter, such as the cores of pears; pancreatic calculi, which are white in colour, rough, and brittle; intestinal sand; and drug calculi.

Intestinal Sand

Collections of small gritty masses occur sometimes in considerable amounts. These are brown-red, grey, or greenish in tint, and of irregular form. They are generally composed of calcium and magnesium salts deposited upon a matrix of undigested vegetable or fruit debris. Another form is apparently deposited *in situ* in mucous colitis. Here there is no organic basis.

Drug Agglomerations

These are seen occasionally when salol, magnesium carbonate, calcium carbonate, bismuth subnitrate, or sulphur have been ingested.

Concretions.

Enteroliths and coproliths are hard masses composed of undigested food debris mixed with deposits of magnesium and calcium salts or fatty acids. The former come from the small intestine and are light in colour, small, sometimes faceted, but frequently round in shape. Coproliths are found in the large intestine, are larger, harder, and of greater mass, and usually in shape resemble that of a fragment of formed stool.

INTESTINAL ANIMAL PARASITES

For the sake of conciseness and in spite of slight inconsistency in classification, the microscopical as well as the macroscopical description of intestinal parasites is included in this section.

The common animal parasites and saprophytes whose ova or adult forms appear in the human intestine are:

I. Protozoa.

(*a*) **Amoebae**
- *Amoeba coli communis.*
- *Entamoeba histolytica.*

(*b*) **Flagellates**
- *Trichomonas intestinalis.*
- *Lamblia intestinalis.*
- *Cercomonas hominis.*

(*c*) **Paramoecium** *Balantidium coli.*

II. Metazoa.

(*a*) **Platyhelminths.**

Trematodes
- *Schistosoma mansoni.*
- *Schistosoma japonicum.*
- *Schistosoma haematobium* (Bilharzia).

Cestodes
- *Taenia solium.*
- *Taenia mediocanellata.*
- *Bothriocephalus latus.*
- *Taenia cucumerina.*
- *Taenia nana.*

(*b*) **Nematodes**
- *Strongyloides stercoralis.*
- *Trichocephalus dispar.*
- *Trichina spiralis.*
- *Ankylostoma duodenale, Necator americanus.*
- *Ascaris lumbricoides.*
- *Oxyuris vermicularis.*

A number of other varieties native to animals have been described as occupying a human habitat, but such cases are very rare.

Amoebae

Amoeba coli communis is found not infrequently in warmer climates. It is non-pathogenic.

Entamoeba histolytica is the cause of amoebic dysentery. The amoebae are motile, of a diameter of 35 μ, and, a point of great importance in diagnosis, contain red blood corpuscles. The cysts measure 7–12 μ and contain only four nuclei (see p. 196).

Amoebae and cysts may be present in the absence of dysentery. When signs and symptoms suggestive of a liver abscess are present in a patient who has travelled in the tropics the presence of cysts may be of diagnostic value. Stools should be examined as soon as possible after being passed (see p. 197).

Flagellates

There is some doubt as to the pathogenicity of trichomonas and cercomonas. It is probable that unless they are present in very considerable numbers no symptoms directly ensue, but that in the presence of diarrhoea they may under such circumstances be held responsible.

The precautions taken for amoebae should be taken in their isolation, and the stool should be examined as soon as possible after passage.

The cysts are present in the stools in greater number than the parasites. Three negative examinations, if thoroughly carried out, are exclusive.

Lamblia intestinalis is not found in the mature form in the faeces unless severe diarrhoea exists. The cysts are to be found in all cases, sometimes in considerable numbers. The organism probably accentuates a pre-existing diarrhoea more often than it initiates symptoms.

Paramoecium

Balantidium coli is a paramoecium which generally infects men through contact with the faeces of swine. It is commonest in Scandinavia and Russia. The symptoms are those of diarrhoea and sometimes of severe anaemia. An eosinophilia has been described. The stools may be found to be swarming with the motile bodies.

Platyhelminths

Schistosoma japonicum. This worm is 1–2 cm. in length, inhabits the portal venous system, is common in Japan, and gives rise to serious symptoms. Its presence is diagnosed by the discovery of ova in the faeces.

Schistosoma haematobium (Bilharzia). The normal habitat of the adult worm is the portal or mesenteric veins. The symptoms, which are referable to the local presence of multitudes of ova, are those of haematuria or diarrhoea; the lesions present are ulceration and polypoid proliferation of the vesical or lower colonic and rectal surfaces. The specimen of urine richest in ova is the last drop squeezed out at the end of a normal act of micturition.

The Pathological Findings are:

I. The Presence of the Ova in the Urine or Stools.
II. The Presence of the Ova in a piece of polypoid Mucosa removed by sigmoidoscope.
III. Haematuria, slight or severe, without evidence of a renal lesion.
IV. The Presence of Blood and Mucus in the stools.
V. Sometimes an Eosinophilia.

Cestodes

Taeniae. The presence of tape-worms, of whatever kind, is proved by the passage of *proglottides* and of *ova* in the stools. Three negative examinations exclude their presence, unless the worm is immature or partially removed. After ineffective treatment it frequently happens that the head and a string of immature segments remain. In this case the previously observed passage of *proglottides* and *ova* comes to a halt until an adequate period has passed. Their absence cannot therefore be taken as necessarily indicating successful treatment.

Should they, however, remain undetected by the end of ten weeks after treatment, although carefully searched for, the probability is that expulsion of the parasite has been complete.

Detection of the head in the stools probably indicates a cure, for infection is usually single. The stool is passed into a bed-pan containing warm water and covered with a sheet of muslin.

The blood picture in cases of taenia infection may show an eosinophilia, but it frequently does not. An anaemia (p. 117) is sometimes present in bothriocephalus infection.

The larval form of *Taenia solium*, *Cysticercus cellulosae*, has been met with in the skin, heart, liver, brain, eyes, and other positions in man, where it forms small nodules. The cysticercus stage is more frequently accompanied by an eosinophilia.

Nematodes

Strongyloides stercoralis is rarely found in temperate climates, but is fairly common in the East. It is the cause of Cochin-China diarrhoea, producing a mild enteritis and a slight anaemia.

The embryo forms are present in large numbers in the stools and the ova occasionally.

The parasite may be associated with *Ankylostoma duodenale.*

Trichocephalus dispar, or the whip-worm, is not uncommon. It lives chiefly in the caecum, the adult forms

being rarely found in the faeces. The ova are always to be found if carefully sought for. Three negative examinations can be taken as excluding their presence. Since the symptoms are frequently slight or absent the parasite often escapes notice; less frequently, however, anaemia, enteritis, and diarrhoea are directly ascribable to its presence. An eosinophilia is suggestive if it is present.

Trichina spiralis produces symptoms by two distinct processes. After ingestion of the embryos in insufficiently cooked pork, these attain adult life, and the females become impregnated, the males dying and being passed in the stools, where they may very occasionally be found in the early stages. The female worms live in the gut for 6–8 weeks, during which time large numbers of embryos are set free into the intestinal canal. Most of these only succeed in irritating the mucosa, setting up a condition of enteritis not infrequently associated with fever and the passage of mucus and possibly of blood. Some others may penetrate the mucous membrane and reach the local lymphatics and veins, whence they become generally diffused throughout the body and eventually reach the muscular and intermuscular tissues, producing muscular pain and swelling associated with fever.

A very well marked eosinophilia, as high in some cases as 70 per cent., is an almost invariable accompaniment. Absence of such an eosinophilia makes trichiniasis unlikely as a diagnosis. The degree of eosinophilia is proportional to the severity of the infection. There may in addition be a general leucocytosis.

Biopsical examination of a piece of affected muscle will in most cases confirm the diagnosis, but a negative result does not necessarily exclude it. The disease is self-limited after a period of about eight weeks.

Ankylostoma duodenale, or the American form *Necator americanus*, manifests itself by the presence of severe anaemia (p. 116). Its presence can be proved or excluded by three examinations of the stools, preferably after a saline purge, for the presence of ova.

The effect of treatment can be judged by similar ex-

aminations for ova by a concentration method, and by careful search for the expelled worms, which are quite small in size, the larger female measuring less than 2 cm. in length. Occult blood is present in the stools.

Ascaris lumbricoides is common, especially in children. The ova are to be found in every case. An eosinophilia may occur, but is more often not present.

Oxyuris vermicularis, or the threadworm, is more frequently noticed in its adult form, either in the motions or in the neighbourhood of the anus. The ova are not commonly found in the faeces, but can be readily obtained from beneath the finger-nails or by scraping the anal mucosa, where the adult female worm is generally to be found.

Blood and mucus may appear in the faeces, and result from an associated acute enteritis.

HYDATID DISEASE

Hydatid disease cannot be described as a disease of the gastro-intestinal system. It is placed beside the other animal parasites for the sake of convenience.

Taenia echinococcus normally is present in the intestines of the dog. Its cystic stage occurs generally in the sheep, infection being retransferred to the dog by way of infected meat. Occasionally man is infected, and under these circumstances the cysts are usually localized in the lung or liver, though other sites are less frequently occupied by the parasite.

To the clinical and radiological diagnosis of the condition laboratory methods can lend considerable aid.

The most useful are:

I. The Casoni reaction.
II. The complement fixation test.
III. An eosinophilia.
IV. Examination of the hydatid fluid.

Casoni (5) in 1911 showed that a cutaneous test similar to the Pirquet reaction for tuberculosis, and carried out with hydatid fluid as an antigen, was positive in seven out of twenty-five cases. Dew and Kellaway (6) have modified the test and use an intradermal method. Their antigen is

hydatid fluid obtained aseptically from infected sheep. It is stored in small sealed ampoules on ice, and keeps, apparently, for at least six months. The amount injected is 0·2 c.cm. intradermally, and a control injection of saline is also made. The saline wheal soon fades, that made by the hydatid fluid increases in size by pseudopodial extensions and may grow to a diameter of 5 cm. It is usually maximal in 15–20 minutes, and is surrounded by a zone of erythema 4–5 cm. wide.

This immediate reaction may be followed by a late reaction consisting of a large erythematous and even indurated area, often simulating cellulitis and appearing after an interval usually of about 12 hours, and lasting for a further 12–24 hours. These two reactions, the early and the late, must be distinguished, for they give information of different natures, though Dew regards them as both resulting from a single cause. In conditions simulating hydatid disease, such as ovarian cysts, enlargement of the liver, abdominal neoplasm, phthisis, intrathoracic neoplasm, pleurisy, and syphilis of the lung, the early reaction has been found to be negative. In 92 per cent. of cases of proved hydatid disease the early reaction is positive. Should suppuration not have occurred the late reaction is generally also positive, but should it have occurred the late reaction is usually negative. Similarly degeneration and calcification of the cyst generally produce a disappearance of the late reaction.

Dew summarizes the facts as follows:

I. The intradermal reaction in hydatid disease presents two phases, an 'immediate' urticarial wheal and a 'delayed' erythema and oedema of the subcutaneous tissues. The former is the essential feature of the reaction.

II. In carrying out the test it is important that the injection should be intradermal, and the patient should be observed for the first half-hour and at the end of twenty-four hours.

III. The test is specific, although care has to be taken to provide controls and some experience in interpreting it is necessary to avoid pseudo-positive readings.

IV. In pre-operative or doubtful cases the test is of

extreme value. In uncomplicated cases it is much more reliable than the complement fixation test, giving 92 per cent. of positive findings.

V. Suppuration or rupture does not cause disappearance of the power to react, but the delayed phase is inhibited or suppressed.

VI. In post-operative cases the test remains positive in all patients and even in cured patients may yield a reaction sixteen years after operation.

VII. There is great variation in the type of response immediately after operation which is difficult to explain in the present state of our knowledge.

The complement fixation test appears to be of less value than the intradermal reaction. It is positive in a smaller percentage of proved cases. It is frequently negative when the former is strongly positive; the converse, however, may occasionally be true (7).

A positive result is thus of value, but a negative one is not exclusive.

An eosinophilia occurs in many cases, especially in early infection and when there is a leakage of cyst fluid. A definite eosinophilia is a point suggesting *inter alia* the presence of an animal parasite, possibly hydatid; its absence does not exclude hydatid disease.

The hydatid cyst contains fluid having certain physical and chemical characteristics, also hooklets and scolices.

The fluid is neutral in reaction, a little opalescent; its specific gravity is 1,002–1,015; it contains mucin but no albumin, some reducing substance, and a little sodium chloride. In very old cysts cholesterin is present.

The hooklets are as a rule not discovered by the pathologist except in fluid from a cyst or occasionally in sputum (see p. 243).

MICROSCOPICAL FAECAL CONTENTS

Microscopical examination of the stools is a measure of great value, and for non-bacteriological purposes that of the fresh specimen is more helpful than is that of the fixed and stained preparation.

Fats

Fats are present in the stools as free fatty acids, soaps, and neutral fat. The first of these are the result of the action of the pancreatic lipolytic ferment upon the neutral fat, and the soaps are the result of combination of the fatty acids with sodium, potassium, calcium, and magnesium salts.

Normal stools of adults contain a few soap masses. Fat droplets indicate the previous ingestion of olive or castor oil, or the presence of a pathological deficiency in fat digestion due probably to pancreatic disease. Owing, however, to the lipolytic properties of some of the intestinal organisms the absence of fat droplets or unsplit fat does not exclude pancreatic disease.

The fats normally comprise from 15 to 25 per cent. by weight of the dried stool, neutral fat being 1–2 per cent., free fatty acid 9–13 per cent., and combined fatty acid 10–15 per cent. by weight of the dried faeces. The ingestion of paraffin, castor oil, crystolax, and similar laxatives vitiates the result of analysis. Diarrhoea has a similar effect.

In biliary obstruction the stools contain a considerable mass of split fats and of their soaps that have remained unabsorbed. The same is true of sprue and of coeliac disease (p. 207). In pancreatic disease the excess of fat is the unsplit neutral fat. Quantitative chemical estimation is the only reliable method of judging of abnormalities in fat content.

Vegetable Tissue

Vegetable tissues occur in quantity in most stools, and no definite deductions can be drawn from the amount present or from the stage of digestion.

Starch granules are rare in adult stools, though not uncommon in those of infants fed on some artificial foods. They occur in pancreatic inadequacy.

Mucus

Microscopically mucus is an amorphous, transparent material. Bile-staining suggests an upper intestinal origin, as does intimate admixture with organisms and debris.

The presence of hyaline cells suggests a colonic and of leucocytes an inflammatory affection.

Cells

The cells to be found in the stools, apart from those ingested, are:

Epithelial Cells.
Leucocytes.
Erythrocytes.
Tumour Cells.

Epithelial cells are normally to be found in small numbers, but even so are generally semi-digested. In large numbers they are significant of a catarrhal inflammatory condition of some part of the tract. Stratified squamous cells indicate an anal, and the cylindrical type an intestinal, origin. Decomposition and digestion changes generally make a closer localization impossible, but definite bile-staining suggests an upper intestinal lesion.

Leucocytes are rarely found in normal faeces. Their presence in quantity suggests ulceration of the surface of the gut, or perforation of an abscess into its lumen (p. 173). The cell present as a rule is the polymorphonuclear, but in helminthiasis and in some forms of mucous colitis and in food allergy the eosinophile is found. In bacillary dysentery the presence of the **macrophage cell** is important.

Erythrocytes, unless the bleeding has been colonic or rectal, are rarely present as definite bodies.

Tumour cells are occasionally present in clumps or masses.

BACTERIOLOGY OF THE STOOLS

General Considerations

The stools are formed largely of bacteria, living or dead. It has been estimated that 50,000 millions are passed each day by a normal adult. Since the body temperature and the type of food-supply are ideal for their development it is not surprising that within a few days of birth there are already present many varieties. Normally these are merely saprophytic; moreover, it is probable that the metabolic activity of certain varieties is of actual benefit to the host.

In order that deductions may be drawn with any degree of accuracy from a bacteriological examination of the faeces a clear conception should be held as to the conditions at the different levels of the intestinal tract and as to the factors that produce variations in them.

The **stomach** receives in the food, and from swallowed saliva, sputum, or muco-pus, a large number of organisms. Unless these are contained in fluid which is ingested when the stomach is empty they are completely destroyed by the hydrochloric acid. In the former case some of the fluid passes unsterilized into the duodenum.

Achlorhydria always predisposes to infection by means of the food; should an alveolar, naso-pharyngeal, or pulmonary infection coexist the danger is intensified. Hurst considers this the probable mode of causation of pernicious anaemia.

Duodenal Bacteriology has become of greater interest since the introduction of the duodenal tube. Organisms present in the gall-bladder, for example *B. typhosus* or *B. paratyphosus*, can be isolated in pure culture from carriers of the infection. This investigation is necessary before cholecystectomy in such cases is justifiable.

Calmette has shown in calves that a generalized tuberculosis is accompanied by the presence of many organisms in the bile. Inoculation of the latter into guinea-pigs is a measure worthy of investigation in suspected cases of human generalized infection. The duodenum may also be expected to contain from time to time a few naso-pharyngeal organisms that survive the gastric hydrochloric acid.

The small intestine is the first favourable culture chamber entered by swallowed organisms or by those excreted in the bile. Direct investigation of it in the living human being is not easy, but certain results have been obtained and certain deductions may legitimately be drawn.

The three factors influencing its bacteriology at any given level are:

1. The Number of Bacterial Invaders.
2. The Presence of a Congenial Pabulum.
3. The Mechanical or Physical Factor.

The number of bacterial invaders from above depends directly upon the number escaping stomach digestion and the number excreted in the bile. The number of invaders from below probably depends upon the rate of the downward stream and the health of the intestinal mucosa. In the case of motile organisms attempting to ascend from their breeding ground in the ileum and large intestine, the success of the invasion must largely depend upon the rate of the stream. When, however, stasis, catarrh, or lack of vitality of the mucosa is present, it is probable that the accumulation of mucus, and even the invasion of tissue, presents lodging points by means of which the infection of levels normally relatively sterile is made possible.

Bacteriological investigations upon the intestinal contents of normal human beings killed as a result of accident, and upon dogs, whose flora is reasonably like that of man, have shown that the flora varies greatly at different levels in the intestine in one individual. From this it follows that variations in the rate of the bowel movements alone, whether produced pathologically or as a result of a purge, will inevitably produce a marked change in the picture. This should be remembered when attempting to assess a report upon the bacteriology of a stool that has been obtained, as is generally the case, after a saline purge. Normally the small intestine contains very few organisms in its upper few feet; those present are generally *B. welchii* and a few Gram-positive cocci. The lower feet of the jejunum contain a similar though rather less scanty population. The ileum in its upper part contains many *B. welchii* and similar anaerobes and a fair number of *B. coli*; in its lower part it becomes the most densely inhabited area in the intestinal tracts, *B. coli* being more numerous than other types, streptococci also occurring in greater numbers here than elsewhere, but *B. welchii*, probably as a result of the acidity produced by *B. coli*, becoming much less in evidence.

The caecum and large intestine contain a very large number of organisms, more particularly in the proximal part where the faeces are still fluid or fairly moist. In the distal section and rectum, probably as a result of dehydra-

tion, the proportion of dead to living organisms rises rapidly. In the proximal section the predominating inhabitant is still *B. coli*, though it is less in number than in the ileum. The streptococcal content becomes much less as the descending colon, sigmoid, and rectum are reached.

In connexion with these statements it must be remembered that the experimental evidence quoted is cultural and therefore incomplete, and that a stained faecal film only gives a picture of the organisms whose living or dead bodies have emerged from the rectum undisintegrated.

The intestines contain many other types of organism, but little is known about them.

THE DETERMINATION OF THE FAECAL FLORA

There are two main motives for bacteriological examination of the stools. Either an attempt is being made to explain symptoms, gastro-intestinal or remote, as being due to an unknown intestinal infection, or else proof of the presence of some particular pathogenic organism is being sought.

General Bacteriological Investigation of the Stools

The former investigation is usually prompted by the persistence of intestinal symptoms, or by the absence of an obvious cause for such conditions as polyarthritis, 'rheumatism', or pyrexia of unknown origin for which an infective basis is suspected. In this case a film stained by Gram's method is an essential part of the investigation, and a definite preponderance in it of some organism, even though cultures do not seem to bear out the same conclusion, is occasionally suggestive.

It is desirable to spread and to fix the film as soon as possible after passage of the stool, for in this way there will have been no time for bacteriological growth to have proceeded outside of the body, a contingency which, unless the specimen is kept cold, is likely to occur. Cultures may show an abnormal flora in one of two ways: either some known pathogenic bacterium is isolated, or there is a change from the normal relative proportions of the usual inhabitants.

THE SIGNIFICANCE OF FAECAL BACTERIA, AND THE FACTORS INFLUENCING THEIR PRESENCE

An organism may be significant in the faeces either by its predominance in unusual numbers or by its mere presence. Predominance of a potentially pathogenic organism is the result of a diet favouring its growth, of continued ingestion, or of continued infection from a focus in the alimentary tract.

The pathogenic organisms whose presence at all is significant are:

B. typhosus.
B. paratyphosus A, B, and *C.*
The dysentery group of bacilli.
Gärtner's bacillus.
Morgan's No. 1 bacillus.
B. aertrycke.
B. psittacosis.
B. botulinus.
The tubercle bacillus (see p. 194).
The cholera vibrio.
Actinomyces bovis.

Purely saprophytic organisms are:

B. faecalis alkaligenes.
B. prodigiosus.
B. acidophilus.
B. bulgaricus and other lactic acid bacilli.
B. pyocyaneus.

A. Organisms whose Predominance is Suggestive

Predominance of certain organisms in the stools is often secondary to particular types of diet; moreover, the organisms present in the intestine fall into two main groups according to whether they are mainly fermentative or mainly putrefactive. The first group contains *B. acidophilus*, *B. bifidus*, and *Streptococcus faecalis*, and the latter *B. welchii* and *B. aerogenes capsulatus*. The *B. coli communis* facultatively belongs to either group according to the nature of the food taken.

A diet rich in meat and eggs favours the proteolytic or putrefactive organisms, one rich in carbohydrates the fermentative group. Clinical use can be made of this knowledge in two ways: either it will explain the presence of a certain bacteriological picture, or it will give a hint as to how a change in the picture can be produced. Certain very definite symptoms result from the predominance of putrefactive organisms in the intestine (p. 193), and a change in the flora is followed by relief.

The carbohydrates most effective in changing a putrefactive flora to a fermentative one are lactose and dextrin (8). The amount of lactose necessary to change the flora in an adult is 4–8 ounces per diem, and the diet should be rich in other carbohydrates such as toast. Fat and protein should be cut down, and the lactose should be suspended in milk and flavoured with vanilla. Some transitory and slight abdominal distension may occur at first. A diet rich in vegetable proteins, such as are present in peas and beans, is also likely to cause a great diminution in *B. welchii* and other putrefactive organisms.

As an accessory to either of these diets *B. acidophilus* cultures can be swallowed at the commencement of the treatment. An emulsion of the live bacilli obtained from a pathologist should be taken on an empty stomach in three-quarters of a pint of water for four consecutive mornings. The *B. acidophilus* tablets on sale are of doubtful value.

Streptococcus pyogenes and staphylococci are occasionally present in large numbers owing to the rupture into the gut of an abscess.

B. Organisms whose Presence at all is indicative of a Pathological Condition

The presence of *B. typhosus* or *B. paratyphosus* in the stools indicates either a recent infection or the presence of a chronic typhoid cholecystitis (p. 185).

Dysentery bacilli (Shiga or Flexner) are only found in active dysentery, in carriers, or in rare cases of chronic colitis.

Gärtner's bacillus and *B. aertrycke* are the causes of an acute disease characterized by an enteritis and by general symptoms (p. 191); their presence in cases of enteritis is transitory, but in carriers is often of long duration.

Morgan's No. 1 bacillus is present in some cases of acute enteritis in infants; it is occasionally found in adults.

B. psittacosis is the cause of a septicaemia attacking parrots and is transmissible to man. The onset is acute, and the pyrexia and general condition suggests typhoid fever. Diarrhoea may be present, and later bronchitis and bronchopneumonia occur. The organism can be isolated from the blood in the earlier days, and later from the stools and sputum.

B. botulinus is only found in man in cases of botulism. It can be isolated from tinned goods or other foods concerned in an outbreak of the disease. It is generally present in spore form (see p. 192).

Vibrio cholerae. The microspira, comma, or cholera vibrio is present in all cases of cholera. Special cultural and serological tests are necessary for its exact identification. It is not found in the blood or urine. It may be present in the stools of carriers.

Actinomyces bovis. This organism in its filamentous form may be present in the stools in abdominal actinomycosis, but it is generally not easy to discover and more frequently is obtained from an abscess either at a laparotomy or from a discharging fistula (see p. 68).

CHAPTER XIII

DISEASES OF THE INTESTINES

'FOOD POISONING' OR INFECTIVE ENTERITIS

Food poisoning, once termed ptomaine poisoning, is the result in the great majority of cases of the contamination of food by certain pathogenic bacteria. The commonest of these are *B. paratyphosus*, *B. enteridis* of Gärtner, *B. aertrycke*, and *B. suipestifer*, and other closely allied members of the coli-typhoid group. Less commonly, *B. botulinus* is responsible. The two groups differ in several respects.

Gärtner or Salmonella Group

The common sequence of events is that the contaminated food has been kept warm at a temperature suitable for the multiplication of the organisms before it is taken; prepared flesh foods, such as brawn or sausages of pork or beef, are generally to blame. From six to twelve hours afterwards acute abdominal pain, with vomiting and diarrhoea, attacks the participants of a meal. It is remarkable that the food is generally not decomposed or changed in smell in any way, and only by laboratory means can the source of infection be traced.

Pathological Findings

I. Presence of the Organism in the Food.
II. Presence of the Organism in the Blood, Urine, and Faeces of the Patient.
III. Presence of Agglutinins in the Blood-serum.
IV. A transient Erythrocytosis, of a degree varying with the dehydration produced by the diarrhoea and vomiting.

Isolation of the same organism from both patient and food is conclusive evidence as to the nature of the illness. The organism is probably present in the blood in most cases at the onset of illness, but a positive blood-culture is by no means the rule. A negative result does not exclude the diagnosis.

The organism is obtainable from the urine in a greater percentage of cases during the first seven days or so of the illness, and for the same period is even more easily isolated from the stools.

Negative cultural results from stool, urine, and blood during the first few days make the diagnosis of food poisoning of the enteritidis type very unlikely. The organism has generally disappeared from the excreta after ten days.

The presence of agglutinins in the blood generally follows an attack, but is not found for the first few days. After the lapse of a week agglutinins against the causative organism are generally present. The following facts, however, make agglutination alone uncertain, except in the case where the patient's serum is found to agglutinate a non-lactose fermenting bacillus from his own stool or urine. The members of the Gärtner group are very numerous, and the homologous emulsion may not be obtainable. Cross-agglutination is a common property of its members. Previous inoculation with T.A.B. may vitiate the result. Should agglutination be obtained variation in the titre after a few days indicates a recent infection. The dilution to which agglutination is obtainable is much less in the food-poisoning organisms than in true typhoid or paratyphoid fever, figures of only 1 in 50 being not uncommon. A positive result is thus of value, but a negative one is not conclusive.

BOTULISM

The method of infection is similar in the case of botulism to that occurring in the Gärtner group, but the incubation period is generally longer (24–48 hours); moreover, the food is frequently tainted. Finally, owing to the fact that the optimum temperature for its growth is below that of the body, and that at body temperature little toxin is produced, the disease is really due rather to the absorption of a large dose of already present exotoxin than to the proliferation of organisms inside the intestine. The food is poisoned but the patient not infected.

The following laboratory tests are of value in the diagnosis.

I. The food should be sent to an expert for animal inoculation, and to determine the presence of spores. Only in this way can the causative organism be discovered.

II. Spores may be present in the stools, and the organism can in some cases be thus isolated from them, but the diagnosis must be made clinically.

Treatment

Exact isolation of the organism, preferably from a sample of the food, is necessary. There are two varieties of organism, A and B. A di-valent antitoxin has been prepared which is efficacious provided that its administration is sufficiently early after infection. The serum should, therefore, be given on clinical grounds alone, while awaiting the pathological report.

PUTREFACTIVE INTESTINAL INDIGESTION

Protein putrefaction occurs to some extent in the intestine of normal individuals. When an excess of protein is taken or when for some other reason the growth of the organisms concerned, of which *B. welchii* is an important example, is encouraged, putrefaction is apt to occur to a degree that may cause symptoms such as headache and considerable lassitude.

The body whose presence is most indicative of this condition is indican, an oxidation product of indol; and the stools show an excess of the putrefactive organisms. Indicanuria is particularly suggestive of disease of the small intestine; such disease may be acute, as in acute intestinal obstruction and typhoid fever, or chronic, as in less defined types of dyspepsia. It may also occur when albuminous tissue is being decomposed in other areas of the body, such as the lung in empyema, abscess, and putrid bronchitis. The amount of ethereal sulphate present in the urine is normally less than 0·3 of a gramme of sulphuric acid in an adult.

The bacterial findings and their variation with the type of food are referred to on p. 189.

TUBERCULOUS ENTERITIS

Tuberculous ulceration of the intestine is not associated with any distinctive pathological findings. Examination of the stools may be negative or positive. The positive results are:

I. The Presence of Occult Blood.
II. The Presence of Tubercle Bacilli.
III. An Excess of Fat.

The absence of occult blood makes an open ulcerative lesion unlikely; its presence is suggestive only if other sources, such as swallowed sputum and bleeding gums, can be eliminated.

Tubercle bacilli may come from two sources other than intestinal ulcers, namely the bile or swallowed sputum. Their presence in large numbers, provided that sputum is ejected and not swallowed, is suggestive, particularly if they are present in bile-stained mucus.

An excess of split fat is not uncommon in children with tuberculous enteritis or peritonitis. The reason is to be found in impaired absorption.

SPRUE

Sprue is a disease whose main symptoms are soreness and ulceration of the mouth, frequent foamy or frothy stools, wasting, diminution in the size of the liver, and anaemia.

The cause is unknown, but is thought by Ashford to be due to infection by a monilia. This hypothesis, like most others, has not met with general acceptance.

The Pathological Findings are:

I. Chemical Changes in the Stools.
II. A Progressive Anaemia.
III. A Lowered Blood-calcium Value.

The stools show some small degree of both liver and pancreatic inadequacy, together with an excess of fermentation. They are frothy, pale, and contain many undigested muscle-fibres and an excess of fat which in acute sprue may comprise

50–60 per cent. of the dried stool. Most of this is in the form of split fat and chiefly as free uncombined fatty acid. The deficiency seems therefore to be one of absorption rather than of digestion.

The anaemia in young adults is most often chlorotic in type, but in older patients not infrequently resembles that of pernicious anaemia. The haemoglobin is often nearly unity and sometimes above this. The red cell count may fall to below 1,000,000. There is a leucopenia which is largely polymorphonuclear. A positive indirect van den Bergh's test is frequently present.

APPENDICITIS

Appendicitis is due to infection of the appendix by organisms, the commonest invaders being *B. coli communis* and streptococci.

These are normal inhabitants who have taken advantage of a lowered resistance on the part of the appendicular tissues. Factors helping their invasion are:

1. Enteritis.
2. Possibly constipation.
3. The presence of foreign bodies such as enteroliths, threadworms, cherry stones, &c.

The diagnosis must be made upon clinical grounds, but pathological investigations give help in both diagnosis and prognosis.

The Blood-count in Appendicitis.

Particular attention has been paid recently to the total and to the differential white blood counts in the diagnosis and in the prognosis of acute appendicitis.

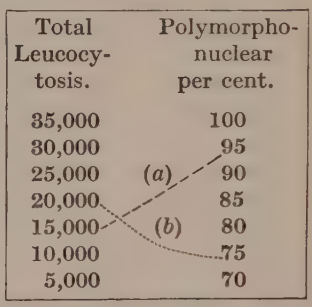
Leucopenia probably eliminates the presence of an acute appendicitis except in exceptionally severe and fulminating cases. Here, however, a comparison between the total and the differential counts will probably give information of value.

A Leucocytosis (of the degree of about 15,000 in an average case) is generally found. Higher figures than this are not usual unless an abscess be also present. In the early stages

lower figures often occur, and it is then that a simultaneous differential count and a comparison of both results may give valuable help.

Three conditions, especially in children, have not infrequently to be differentiated from acute appendicitis. They are lobar pneumonia, typhoid fever, and tuberculous peritonitis. The first of these is accompanied by a considerably higher leucocytosis (see p. 23) and the second by a leucopenia. The third is dealt with below. The differential white count, as regards the polymorphonuclear content, will give help in estimating the severity of the attack when contrasted with the total leucocyte number.

Gibson (9) has constructed a chart giving total leucocyte figures and polymorphonuclear percentages side by side, as shown in the figure. Should the polymorphonuclear percentage be higher in the chart than the corresponding total figure the attack is assumed to be of considerable severity in proportion to the slope of the line (*a*). If the line is horizontal the patient is probably holding his own, and if it is falling the infection is mild (*b*).



A normal eosinophile count also indicates a mild lesion.

AMOEBIC DYSENTERY

Amoebic dysentery is the result of infection of the intestine by *Entamoeba histolytica*. This invasion is sometimes devoid of serious symptoms, in which case it may remain latent and be forgotten; occasionally, however, an amoebic liver abscess develops later in a patient who is unable to recall the primary dysentery. Carriers of the amoeba occur, and it is largely to them that cases of the disease are due. Infection is generally through the cystic form of the amoeba.

Amoebic dysentery occurs in definite stages:

1. The acute dysenteric stage.
2. The chronic ulcerative stage.

The acute stage may be a transient and determinate disease or may give place to a long-continued illness. This can take the shape of a chronic constipation with some added intestinal discomfort or of a severe chronic colitis. In either form acute exacerbations are not uncommon. The stools in the acute stage are for a few hours faeculent, then slimy containing mucus, and later muco-purulent or sanguino-purulent. In the chronic colitic stage they are a watery mixture of faecal material, mucus, and flecks of blood.

The Pathological Findings are due to the presence of the amoebae and to the reaction of the intestinal tissues against them. They can be tabulated as follows:

I. The Presence of *Entamoeba histolytica* or its Cysts in the Stools.

II. Blood, Mucus, and Charcot-Leyden crystals in the Stools.

III. Concentration of the Blood, due to Diarrhoea.

IV. A Secondary Anaemia with some slight Leucocytosis.

I. **Amoebae** are present in the acute stages in the large motile trophozoite form and contain red blood-cells. When the disease persists in a subacute form fewer of these and more of the encysted organisms are found. Finally, in the intervals between exacerbations, or in carriers, the cysts only are to be discovered.

Three examinations of the stool at least must be negative before the disease can be excluded, and it should be remembered that mucus is more likely to contain the amoebae and faecal matter the cystic forms. The stool should be examined fresh, and if possible warm, by the pathologist; indeed, in ambulatory cases the patient should be sent to the laboratory in person. A stool can then be obtained and examined on the spot, or a proctoscopic examination may allow of the isolation of motile amoebae from an open ulcer.

II. Macroscopic **blood** and **mucus** are present in the acute disease and in exacerbations, but are frequently absent in the quiescent periods between relapses. Occult blood is always present if there is anywhere an open ulcer.

Charcot-Leyden crystals are very commonly present.

III. and IV. During severe diarrhoea the haemoglobin and red blood-cell count may appear to be normal, but this concentration as a rule masks a considerable underlying **anaemia.** During convalescence the red blood count rises again to normal. In the chronic colitic stage the haemoglobin percentage gives a clue as to the amount of blood loss.

A considerable **leucocytosis,** especially in the chronic form of the disease, should always hint at the possibility of two serious complications. The first of these is amoebic liver abscess, due to amoebic invasion of the liver, and the second is the rarer post-colic abscess, resulting from perforation of a colonic amoebic ulcer and the formation of a localized intraperitoneal abscess which is frequently retrocaecal. Since an acute amoebic hepatitis, however, may occur without suppuration, together with a considerable leucocytosis (12,000–15,000), the latter finding does not invariably denote the presence of pus. The effect of emetine treatment upon both the symptoms and the white count should be watched in doubtful cases.

BACILLARY DYSENTERY

The cause of bacillary dysentery is infection by some member of the group of dysentery bacilli. Contamination of food and drink by flies and carriers provides the most usual mechanism.

The acute and chronic stages, the relapses and remissions, the tendency to the development of a chronic colitic lesion, are analogous in the two cases. In tropical climates a mixed infection by amoebae and dysentery bacilli is not very uncommon.

The Pathological Findings are :

I. The Presence of Bacilli in the Stools and Absence of Amoebae.
II. The Presence of Bacilli in the Blood (occasional).
III. The Development of Agglutinins in the Blood.
IV. Blood and Mucus and Macrophages in the Stools.
V. Concentration of Blood due to Diarrhoea.

VI. A Progressive Secondary Anaemia.

VII. The Presence in the Urine of Albumin and sometimes of Hyaline and Granular Casts.

I. **Bacilli** can be isolated from the stools from the onset of acute symptoms. They are present in every case. Absence of dysentery bacilli, if properly looked for in an acute case, eliminates bacillary dysentery. Apart from the question of diagnosis an exact determination of the particular type of bacillus is of importance from the point of view of prognosis. The Shiga type is generally associated with a far more severe toxaemia and a worse prognosis than is the Flexner strain. With the latter remissions are more frequent. Differentiation of the strains is of less practical importance as regards treatment, for the serum available is generally polyvalent.

For the best results the stool should be very fresh—after a lapse of four hours the percentage of positive results is considerably diminished. A stool containing blood and mucus, particularly the latter, is the best material. If the specimen is to remain uncultured for more than six hours the precaution should be taken of emulsifying it with an equal quantity of N/33 NaOH solution.

In chronic cases the organisms are still to be found, though with less ease. Cunningham found that in apparently normal Hindus a number of dysentery carriers occurred, and that, provided the number of examinations was sufficiently, high organisms could be isolated in nearly every case. Five examinations gave a positive result in 90 per cent. Here again stools containing mucus and blood offer the best chance of success.

The absence of amoebae, if properly searched for in an acute case of dysentery, is a definite point in favour of bacillary dysentery.

II. The presence of a positive blood-culture is rare. When a **bacteriaemia** occurs the prognosis is definitely considerably worse.

III. The presence of **agglutinins** in the blood is of less diagnostic value than it is in typhoid fever, for by the time that the titre rises to a discoverable degree the disease is

already well advanced. Results of agglutination are frequently negative until the second or even the third week. Variation in titre is of greater significance than is one positive result, unless this is a figure of over 1 in 250 in the case of a Flexner and over 1 in 64 in the case of a Shiga infection. Two methods may be used—the patient's serum against a stock emulsion, or a stock serum against the patient's organism, the former being the more usual. Agglutination gives valuable prognostic knowledge by differentiating the type of organism involved.

IV. The **stools** at the onset of an acute attack are largely composed of greyish mucus in which are embedded many red blood-corpuscles and very many swollen polymorphonuclears—far more indeed than in amoebic dysentery—and considerable numbers of macrophage and epithelial cells, single and in rows. Later these epithelial masses get larger, sloughs of ulcers appear, and pseudo-membranous casts of the gut may be seen. The macrophage cells often contain erythrocytes and are therefore liable to be mistaken for amoebae.

In milder or more chronic cases the stools soon become half formed, though still few and small in amount, but blood and mucus persist.

Prognosis

Though the prognosis must be judged chiefly from the clinical evidence it should be remembered that a positive blood-culture is of bad omen, and that a Flexner infection is less severe than is one by Shiga's bacillus.

Treatment

Serum is of great value and should be given as soon after the onset of symptoms as is possible. By its use the course of the attack is greatly shortened, and the mortality percentage much lowered. It should be given in large doses, for little harm can result, and the possibility of neutralizing the bacterial poison by a sufficient dose should not be rejected.

Prophylactic treatment, on lines analogous to those em-

ployed in typhoid, is of definite value. The vaccine should be given in two or three doses at intervals of a week. It can be obtained from reputable firms. Revaccination of individuals liable to exposure is advisable after twelve months. In the case of outbreaks of 'Asylum' dysentery careful examination of the stools of the inmates for bacilli may reveal carriers whose segregation will limit the epidemic. One of the chief values of clinical pathology in directing the treatment of the disease is the early elimination of *Amoeba histolytica* as the cause or as an additional assailant.

MUCOUS COLITIS

An acute form of mucous colitis sometimes occurs in connexion with acute infective diseases, specific fevers, and chronic nephritis.

The symptoms are diarrhoea with much mucus and occasionally a little blood in the stools. Beyond these macroscopic features there are no typical findings.

Chronic Mucous Colitis may be associated with diarrhoea or with constipation. In the former case the pathological characteristics are: I. Absence of any evidence of a lesion of the small intestine. II. The presence of mucus with a little blood in the stools. The blood-cells, both red and white, are in a practically fresh condition. When associated with constipation the mucus present is in thick, ropy masses; it is transparent, not bile-stained, and contains few cells of any kind. The reaction of the stool is often alkaline, and triple phosphate crystals may be found microscopically.

In the 'muco-membranous' form of the disease the casts are tougher and of multifarious shapes, which, however, when floated in water show their tubular form. They may be coloured by blood or faecal material, and may contain many epithelial cells. Eosinophiles may occur in some cases.

The term colitis as applied to this disease is a misnomer, for there is no evidence of inflammation of the intestinal mucosa. There is apparently no infective factor responsible.

CHRONIC ULCERATIVE COLITIS

Ulcerative colitis may occur as a sequela of acute dysentery, whether amoebic or bacillary, or it may be unheralded by any such occurrence. In the former case recognition of the exciting cause may be of considerable therapeutic benefit. The absence of amoebic cysts or of bacilli does not eliminate the possibility of a dysenteric origin.

The main Pathological Findings are :

I. The Presence of Blood and Mucus in an Unformed Stool.

II. A Progressive Secondary Anaemia.

There is as yet no satisfactory evidence as to the presence in ulcerative colitis of any specific infective organism. The work of Bargen (10), claiming a specific coccus as causative, is unconvincing and needs confirmation. On the other hand, evidence as to a prodromal acute colitis is obtained occasionally by the finding of *Entamoeba histolytica* in its cystic form, or by the isolation of a member of the dysentery group of bacilli. The success in some cases of large doses of antidysenteric serum, as advocated by Hurst, is possibly ascribable to this history. Pus is not found macroscopically in the stools, though microscopically leucocytes are generally present in moderate numbers.

A progressive secondary anaemia of the chlorotic type, often severe, is a normal accompaniment of the disease. Estimation of the haemoglobin percentage from time to time gives valuable information as to the condition of the patient.

Transfusion is a valuable therapeutic measure.

INTESTINAL OBSTRUCTION

Acute Intestinal Obstruction may involve the small or the large intestine, and may be due to a mechanical or to a paralytic cause. Examples of the first are : strangulation by bands and adhesions, by Meckel's diverticulum, and strangulation in a hernial sac ; peritonitis is the usual cause of the second.

Where the obstruction is due to paralytic ileus the clinical pathological findings of the peritonitis predominate.

The Clinical Pathological Findings due directly to the obstruction are:

I. Leucocytosis.
II. Faecal Vomiting.
III. Indicanuria (where the small intestine is involved).
IV. Oliguria.
V. Occasionally the Presence of Albumin and Casts in the Urine.

The Leucocytosis is considerable, averaging about 20,000 twelve hours after the onset of obstructive symptoms. A higher count is suggestive of early peritonitis or of commencing gangrene of the obstructed gut.

This leucocytosis is chiefly polymorphonuclear, and the immediate prognosis can be to some extent deduced from the relation between the percentage of these cells and the total white count (see p. 196). Should the white count fall, though the symptoms of intoxication persist or are accentuated, the probability of an advancing gangrene or of a severe peritoneal infection is much enhanced.

The eosinophiles are diminished or absent.

The Faecal Vomit is the result of protein decomposition in the small intestine with the formation of scatol and indol. Should these become regurgitated into the stomach vomiting will result. The vomit will thus contain considerable amounts of indol.

Indicanuria is present in great amount where the obstruction affects the small intestine. The early appearance of this abnormality is particularly suggestive. It must be remembered that obstruction of the large bowel ultimately causes a secondary delay and even obstruction of the small intestine. Thus the later presence of indican in the urine, especially in small amount, is a positive finding from which no deductions can safely be drawn.

The reason why indicanuria is not so intense when the large bowel only is affected may be that the albuminous material present, which is its source, is less in quantity.

Oliguria is generally present, the urine being highly coloured and full of urates. In severe cases albumin and casts, both hyaline and granular, may be found.

CHAPTER XIV

DISEASES OF ASSIMILATION AND NUTRITION IN INFANTS AND CHILDREN

THE NORMAL INFANT

The stools of a normal infant will vary according to whether the food has been breast milk or cow's milk. In the former case the motion is yellow, slightly acid, and without smell; in the latter case paler or more grey in colour, alkaline, and with a slight odour. White curd-like masses are present sometimes. These are composed of fat and are distinguishable from the casein curds of undigested milk.

INFANTILE DYSPEPSIA

Fermentative Dyspepsia.

Fermentative disorders of the infantile gastro-intestinal canal are subdivided by Cameron under three heads: **dyspepsia, intoxication,** and **marasmus.** In the former condition the abnormality is one that produces merely an irritation of the gastro-intestinal mucosa; in intoxication there are superadded symptoms and signs due to the passage of toxic substances from the intestinal lumen to the body; in marasmus the process has become irreversible and probably fatal.

In fermentative dyspepsia the excess of carbohydrates present in the intestine permits increased fermentation by bacterial activity. The fatty acids formed act as irritants to the gastric and intestinal mucosa, producing vomiting and diarrhoea. The buttocks become reddened and even excoriated by the irritative stools. Infections often attack the child in its debilitated condition, but may actually be the exciting cause of a fermentative attack.

The chief pathological change found is in the abnormal condition of the stools. These are excessively acid, green, watery, and sour smelling and often contain curd-like masses of soapy material. Undigested casein curds may be

present, but they are merely symptomatic of the increased rate of peristalsis. Blood in considerable amount may be present, but it will be mixed with faecal material and not with plain mucus as in intussusception.

In addition there may be evidence suggesting the presence of some pyogenic infective condition, such as an acute otitis, a pyelitis, or a pneumonia. The presence of a definite polymorphonuclear leucocytosis is suggestive, but in infants its absence is not exclusive.

INTOXICATION

The best example of intoxication is summer diarrhoea. In this condition the persistent and severe fermentative dyspepsia has so injured the mucous membrane as to allow the passage of toxic substances through this into the blood-stream. These produce fever, restlessness or drowsiness, collapse, rapid loss of weight, and occasionally glycosuria and albuminuria.

The Chief Pathological Abnormalities are:

I. Frequent Green Stools, similar to those found in Dyspepsia.
II. Urinary Abnormalities.
III. A Raised Blood Urea.
IV. A Leucocytosis.

The urinary abnormalities found in some of these cases are:

I. Glycosuria.
II. Albuminuria.
III. The presence of Casts.

The **glycosuria** indicates the presence of a severe form of the disease, but not necessarily a fatal outcome. The **albuminuria** is common and alone has no special significance; when associated with the **presence of casts**, particularly if these are epithelial, the prognosis is considerably graver. Occasionally there is an increase in the blood-urea figure out of proportion to the dehydration. The chance of recovery is less in proportion to the degree of urea retention.

Acute nephritis of a focal nature is occasionally found present post mortem.

A leucocytosis, sometimes as high as 30,000, is not infrequent.

MARASMUS

Marasmus is the clinical name given to a condition where there exists not only an inability to make use of ingested food, but an actual accentuation of the symptoms as a direct result of taking food. The pathological findings are indistinguishable from those of 'intoxication'.

INFECTIVE DIARRHOEA

Occasionally some definitely pathogenic organism such as *B. paratyphosus*, *B. dysenteriae*, or *B. welchii* may be present in the stools and directly responsible for the condition. Here the faeces soon consist of little other than green or brownish mucus mixed with blood and containing microscopically pus and fibrinous fragments.

COW'S MILK DYSPEPSIA, 'DECOMPOSITION'

Overfeeding with cow's milk will produce a type of dyspepsia, described by Finkelstein.

There are two main abnormalities:

I. The Characteristic Stools.
II. The Presence of Indicanuria.

The stools are alkaline in reaction, well moulded, rather dry, putty-like in colour and consistency, and distinctly offensive. Calcium phosphate and soaps are present in large amounts.

Indicanuria is generally present, often well marked, though sometimes absent.

SPASMOPHILIA

Spasmophilia is a condition in which certain signs of an excessively easily stimulated nervous system are present. The cause is probably a draining from the body of calcium salts. This particularly occurs when much milk is taken. It has been shown that some infants, upon a high milk diet,

actually excrete more calcium than is being at the time ingested.

The chief pathological finding is a diminished blood-calcium figure. Instead of the normal figure of 10–11 mg. of calcium per 100 c.cm. of blood the figure is diminished. Should the fall be to about 6–7 mg. clinical symptoms of tetany will occur. Removal of the milk from the diet and other measures taken to increase the blood-calcium content are followed in most cases by a return of the blood calcium to normal.

DISEASES OF ASSIMILATION IN LATER CHILDHOOD

COELIAC DISEASE

Coeliac disease is apparently due to a deficient power of absorbing fats. This becomes manifest as a rule within the second and third years and causes characteristic symptoms. Chief of these is the so-called diarrhoea, the stools being bulky, light in colour, pultaceous, and rancid, but as a rule not more than 2–4 per diem. Their surface is greasy.

Chemically the characteristic abnormality is the great increase above normal in the total fat percentage present. This is in the form of split fats, for pancreatic digestion is not at fault.

A preponderance of unsplit fats is suggestive of some other condition, such as pancreatic inadequacy, and is not found in coeliac disease. An excess of unsplit fats excludes coeliac disease. The fat content is in the neighbourhood of 50 per cent. of the dried stool, of which about 15 per cent. is present as neutral fat, and the remainder as fatty acids and soaps. Stools similar to those occurring in coeliac disease are occasionally to be found when the lacteals are obstructed by tuberculous mesenteric glands.

It must be remembered that diarrhoea alone may cause the percentage of unsplit fats to be unusually high, time for digestion not having been adequate.

No stool should be sent for examination for fat content if the patient has within four days taken liquid paraffin by the mouth.

RICKETS

Laboratory investigations in rickets are very subsidiary to the clinical examination as regards diagnosis and prognosis. Certain investigations, however, are of use at certain stages of the disease, more particularly in prognosis.

The abnormalities occasionally to be detected are:

I. Anaemia.

II. Diminution in Blood Phosphorus and occasionally in Blood Calcium.

The **anaemia** occurs comparatively late in the disease, is of the chlorotic type, and runs largely parallel with the clinical condition. A haemoglobin determination, therefore, in severe cases will, if done at regular weekly intervals, be of some assistance.

Sometimes the so-called von Jaksch's anaemia occurs in infants with early rickets (see p. 127).

The blood-phosphorus content, whose normal figure, according to the method of Bell and Doisey, is about 4·5 mg. per cent., falls early in most cases of rickets. The investigation, however, is not often of great value in practice.

When, as is not uncommon, infantile tetany or spasmophilia is associated with rickets, a low blood calcium is invariable.

With the clinical cure of the disease, whether rickets or tetany, the figures of both phosphorus and calcium return to normal.

'RENAL RICKETS'

Renal rickets is the name given to a condition where the rickety bone phenomena are frequently delayed to a later age than normal before they appear, and which is associated with a type of renal disease analogous in its clinical course to chronic nephritis. This is often unassociated with a nephrosis, and the first manifestations are frequently directly due to renal inefficiency.

The blood urea tends to be raised early, albumin and casts are present in some quantity in the urine. The renal disease is generally progressive and fatal.

Cardio-vascular changes, raised systemic blood-pressure, and cardiac hypertrophy are often present.

ACUTE INTUSSUSCEPTION

Acute intussusception is generally a disease of infants. The invagination of the bowel produces as a rule a complete obstruction to the passage of the bowel contents, their place being to some extent taken below by a considerable outpouring of mucus and blood from the congested and contained piece of gut.

The Chief Clinical Pathological Findings are therefore :

I. The Passage per anum of Blood and blood-stained Mucus.
II. The Absence from the excreta of Urobilin.
III. Absence of a Leucocytosis.

The bowel at first gets rid of its previous contents below the level of the lesion. Thus the first motion is generally faeculent, but this is succeeded by the passage of the blood-stained mucus characteristic of the disease.

The stoppage is usually a complete one, but in rare instances is partial, or recurring and remitting. In the former case urobilin is absent from the later bloody excreta, but in the latter it is probably present.

A slight leucocytosis may be present, but frequently the white blood count is not increased. Absence of a leucocytosis is a point in favour of intussusception.

Differential Diagnosis

The two conditions for which intussusception may be mistaken are acute ileocolitis and Henoch's purpura.

In acute enteritis, though blood and mucus may be present, they are mixed with some faecal material and the stool contains urobilin. Threadworms are not infrequently associated with an acute colitis of this type.

In Henoch's purpura the patient is usually an older child, and again, although blood and mucus may be found in considerable quantity, faecal material and urobilin are also present.

Purpura and possibly haematuria may coexist, and a considerable leucocytosis is common (see p. 134).

CHAPTER XV

DISEASES OF THE PANCREAS

Acute Pancreatitis.
Chronic Pancreatitis.
Carcinoma.

ACUTE PANCREATITIS

An acute inflammation of the pancreas has as a rule too rapid a course to allow of the appearance of signs due either to deficiency of the β-cells of the islands of Langerhans, or to failure of pancreatic intestinal digestion.

The most constant laboratory sign of the disease is an increase in the diastase content of the urine. Normally the maximum figure for this is thirty-two units. In acute pancreatitis the figure is in nearly every case about 100 units, and is very frequently much higher. Absence of an increase is strong evidence against the presence of an acute pancreatitis. It must be remembered that an acute pyrexial attack may cause a slight or moderate increase in the urinary diastase, generally less than 65 and practically always less than 100 (11). A twenty-four hour specimen is scientifically desirable, but examination of the first obtainable sample is, in a matter of emergency, usually clinically sufficient.

A leucocytosis is usual, often of a high degree, but is not absolutely invariable. Glycosuria is rare. If present in a subject known previously to have passed no urinary sugar, there is additional strong evidence as to the presence of a pancreatic lesion.

CHRONIC PANCREATITIS

Chronic inflammation of the pancreas, of whatever cause, produces changes which are most evidently disclosed in the functions of its external secretions. These, whether lipase or trypsin, become inadequate as a result of a much smaller loss of pancreatic tissue than is sufficient for a fully functional insulin supply. Evidence of imperfect digestion of

fats and proteins thus occurs early; glycosuria, if it appears at all, is late. During the process of chronic inflammation, presumably according to the degree of irritation of the gland, an excess of diastase may appear in the blood and concomitantly in the urine.

The Clinical Pathological Evidences that suggest chronic pancreatic disease, whether inflammatory or neoplastic, are therefore:

I. A considerable Increase in the Bulk of the Faeces.
II. Steatorrhoea.
III. Creatorrhoea.
IV. Sometimes an increased Urinary Diastase content.
V. Rarely Glycosuria.

The evidence in the stool of deficient pancreatic activity is due to diminished digestion of the various constituents of the diet. This should therefore be standard. Schmidt advocates—

Breakfast and Tea. { ½ litre of milk. / 50 grammes biscuit or bread.

Lunch and Dinner. { 125 grammes of chopped meat, lightly cooked. / 250 grammes of potatoes. / 100 c.cm. of milk. / 10 grammes of butter.

The commencement and the end of the diet are signalized by the eating of a charcoal biscuit.

The faeces between each blackened motion are collected.

The stools of chronic pancreatic insufficiency are **bulky,** largely as a result of lack of proper digestion and therefore of absorption, and contain often 20 per cent. of the total fat intake.

As well stated by Miller (12), 'the stool of pancreatic disease is large, pale, offensive, and oily. It contains a great **excess of fat**, and its diagnostic feature is the distribution of the faecal fat; a large proportion, over 25 per cent. at least, is in the form of neutral unchanged fat. This shows itself in the stool, if present in large amount, as separated oil or grease which congeals on cooling ("butter-

stühle"); if in smaller quantities, the neutral fat shows under the microscope as oil droplets. This sort of stool does not occur in coeliac disease; there the fat in the faeces is invariably well split.' Similarly, though in bile deficiency there is a lack of proper fat absorption, the fat is normally split. In normal individuals 75 per cent. of the fat is usually split, and 25 per cent. unsplit. In pancreatic insufficiency the figures may be reversed. In children, Harrison (13) states, 'Of the dried faeces not more than one-third should be fat, and of that (faecal) fat not more than one-third should be unsplit, remembering that in infants even one-half of the dried faeces may be fat. Absence of a raised figure for the percentage of unsplit fat makes the diagnosis of chronic pancreatitis unlikely.'

Creatorrhoea

Owing to an associated inadequacy of trypsin, protein digestion is often inefficient. This is best shown by the presence in the stool, upon a meat diet, of **undigested muscle-fibres.** They are best detected microscopically. Diarrhoea and achylia gastrica invalidate the result. A positive finding suggests strongly a pancreatic lesion; a negative finding does not preclude the possibility.

In a certain percentage of cases of chronic pancreatic disease, whether inflammatory or neoplastic, there is an increase in the **urinary diastase** above the normal figure of 30. A negative result gives no help for or against the diagnosis, but a positive one, especially if associated with one or more of the previous findings, is a point in evidence for the presence of a pancreatic lesion; a figure of above 100 is nearly conclusive. The urine should be taken from a twenty-four hour specimen, and can be preserved by adding some toluol.

In advanced cases **glycosuria** may occur. Its presence, especially if associated with one or more of the preceding findings, is a strong point in favour of a pancreatic lesion; its absence is quite inconclusive. Before the establishment of a definite and persistent glycosuria some evidence of diminished sugar tolerance may be obtained from the

glucose tolerance test. The curve will be that of a mild diabetes.

Loewy's test should not be forgotten; here again a negative result is equivocal, and a positive one, especially if associated with one or more other positive pieces of evidence, is of definite value. In addition, an excessive number of starch granules may be present in the stools. An isolated positive result of any of the above tests can do no more than suggest the possibility of pancreatic insufficiency. If two of them are positive the diagnosis becomes likely, and if all are positive it becomes certain.

Jaundice and Pancreatic Disease

Jaundice may be associated with both acute and chronic pancreatitis, and is presumably due to constriction of the common duct by some swelling of the head of the pancreas. In such cases the findings produced by obstructive jaundice are added to the picture (see p. 219).

Chronic Pancreatitis coexists together with cirrhosis of the liver in Haemochromatosis.

Pancreatic cysts do not affect the external or internal pancreatic secretions. They may become secondarily infected, and give rise to signs of sepsis.

CARCINOMA OF THE PANCREAS

General Considerations

The pathological findings in this condition vary with the situation and the extent of the disease.

Should the lesion be small and limited to the head, thus causing obstruction to adjacent hepatic and pancreatic ducts, the findings will be those of obstructive jaundice and of insufficiency of the external pancreatic secretions, either separately or in combination. Should the growth have involved a large area of the gland, hyperglycaemia and glycosuria will result; this, however, is rare. During the process of destruction some excessive liberation of the amylolytic ferment into the blood-stream may occur. A cachexia of a greater or a lesser extent often coexists. Should the growth be localized in the gland away from the

ducts, there may be no clinical pathological abnormalities detectable.

The FINDINGS are therefore:

I. Of Obstructive Jaundice (see p. 219).
II. Of Pancreatic Insufficiency (see Chronic Pancreatitis).
III. Glycosuria.
IV. Increased Urinary Diastase content.
V. Anaemia.

The **glycosuria** will only be found when destruction has involved over seven-eighths of the islets of Langerhans, and thus it is generally anticipated by the patient's death.

The **urinary diastase** is not infrequently increased. A positive result is of some value, more particularly if other positive evidence is available. A negative result does not exclude the disease.

Anaemia of a chlorotic type is common in the terminal stages of the condition.

CHAPTER XVI

DISEASES OF THE LIVER AND GALL-BLADDER

TESTS OF LIVER FUNCTION

General Considerations

It is natural that laboratory tests which give information of liver damage, before this is revealed by clinical evidence, should be eagerly sought after. As clinical evidence of inadequacy of the metabolic functions of the liver only appears when the organ is very extensively damaged and the prognosis practically hopeless, such tests would be of great diagnostic value. Diagnosis of diseases of the liver turns upon the physical signs of gross anatomical change, or of disorder of the biliary function: and since this may exist independently of hepatic disease, it is not to be wondered at that many cases present diagnostic problems of the utmost difficulty.

The numerous functions of the liver suggest almost as many possibilities for liver function tests, and a very large number of these have been investigated. Unfortunately for our purpose, the liver has a big reserve, and even a badly damaged liver may give negative results to all tests of liver inefficiency. It may be stated, with a fair degree of confidence, that the only tests of liver function which so far have proved to be of any value are those relating to the biliary function. These tests of normal formation and secretion of bile are:

1. Tests for the Presence of Bilirubin in the Serum—Fouchet's test: the van den Bergh test.
2. Tests for the Presence of Bile Pigment and Bile Salts in the Urine.
3. Tests for the Presence of Urobilin and Urobilinogen in the Urine.

Their value lies, first, in the possibility of detecting latent icterus: that is, a condition where the serum contains excess of bilirubin, though not sufficient to give

clinical jaundice; secondly, in the help they may give in the distinction between the three main groups of jaundice.

Fouchet's test is a delicate test for the presence of bilirubin in the serum. It consists in placing five drops of the serum in a porcelain dish and adding an equal volume of the reagent.[1] A greenish blue colour appears, reaching its maximum in twenty minutes, in positive cases. By this test bilirubin may be detected in a dilution of 1 part in 60,000. It is therefore sufficiently sensitive to detect latent icterus, and is, moreover, a simple test which the practitioner can readily carry out for himself.

The **van den Bergh test** is, however, more delicate: this is described later under Jaundice (see p. 221).

The significance of **urobilin** in the urine is doubtful. It seems probable, however, that bile pigment, on reaching the intestines, becomes converted into urobilinogen and urobilin, some of which is absorbed, converted back by the liver into bile pigment, and resecreted. Very little, therefore, is normally present in the general blood-stream and urine. Damage to this function of the liver-cells leads to the appearance of urobilin, or urobilinogen, in the urine.

The tests of this group cannot, however, be regarded as adequate tests of liver function. Excess of bilirubin may occur in the serum in the presence of a perfectly healthy liver, and, as has been mentioned, the significance of urobilinuria is uncertain. Moreover, a negative result is no evidence of a healthy liver; it is a not uncommon finding, for example, in some cases of early cirrhosis of the liver. As a guide to the treatment of pregnant women with albuminuria, such tests are probably of little or no value (14).

Of the many other tests of liver function which have been investigated, the laevulose tolerance and galactose tolerance tests are most worthy of mention, and may prove to have some value.

[1] Fouchet's reagent. Trichloracetic acid 5 grammes.
Water 20 c.cm.
10 per cent. $FeCl_3$ 2 c.cm.

The **laevulose tolerance test** is carried out as follows: The fasting blood-sugar is determined. The patient then drinks 50 grammes of laevulose dissolved in 100 c.cm. of water. Blood is collected at half-hourly intervals for two hours, and a blood-sugar estimation is carried out on each specimen. The average normal curve does not show a rise of more than 8–12 mg. above the fasting level, which is reached again in two hours or less. In patients whose liver function is damaged, the rise in blood-sugar is considerably greater, and the value has not dropped to the fasting level in two hours. A rise of more than 30 mg. is to be regarded as abnormal.

In the **galactose tolerance test,** the patient drinks 40 grammes of galactose dissolved in 400 c.cm. of water; otherwise the procedure is exactly as for the laevulose test. With a normal liver function the rise in blood-sugar is never greater than 30 mg. above the fasting value, and this is reached again in two hours. Davies (15) finds marked positive reactions in catarrhal jaundice. He believes that the test may have some value in distinguishing the three main groups of jaundice. In jaundice, due purely to mechanical obstruction, as by a stone in the duct or by carcinoma of the pancreas, the result of the test is negative. It is negative also in cases of haemolytic jaundice, but positive in the toxic and infective group. Variable results were found in cases of cirrhosis of the liver.

It is a common experience, in assessing the results of laboratory tests, that, though we may feel justified in drawing certain conclusions from a positive finding, a negative result rarely proves the converse. The liver function tests afford a good example: marked positive results strongly indicate deficient liver function; negative results are equivocal.

Of other liver function tests the **glycuronic acid reaction,** introduced by Roger in 1916 (16), appears to be of some help in prognosis. Under normal conditions glycuronic acid is formed from glucose by the animal cell, and, it is thought, principally, if not entirely, by the cells of the liver. It is produced apparently for the specific purpose of com-

bining with toxic substances absorbed from the intestines, such as skatoxyl, indoxyl, and phenols. The compound glycuronates which result are harmless, and are eliminated by the kidneys. A great variety of drugs after absorption from the intestines are eliminated in this way: among these are chloral hydrate, salicylates, thymol, turpentine, and camphor. The administration of such substances to a normal man provokes increased excretion of glycuronates.

Roger's reaction for glycuronates in the urine is extremely delicate; it is positive when the concentration of glycuronic acid is as little as 2 milligrams in 1 litre. Glycuronic acid occurs in normal urine; this contains an average of 40 mg. per litre, so that the reaction with normal urine may be quite intense. After forty-eight hours' fasting the reaction becomes negative.

In cases of severe liver damage, as for instance in an advanced case of cirrhosis, the urine does not contain glycuronates, and the camphor test provokes no response, or at most only a slight and transient elimination of glycuronates. This test consists in the administration of a cachet containing 0·5 gramme of camphor; at the same time the patient partakes of starchy and sugary foods only.

Observations indicate that, in liver disorders, when the urine becomes free from glycuronates, and remains free after administration of camphor, the prognosis is extremely grave, a fatal termination invariably following after a short interval.

In obstructive jaundice, caused by a stone, or a growth in the pancreas, glycuronuria is more marked than in the healthy individual. (In the case of a growth, it may disappear during the last eight or ten days of life.) Roger thinks that this is due to excess of putrefactive products absorbed from the intestines.

In catarrhal jaundice glycuronuria is normal or increased at the onset, then it diminishes and may even disappear, to return in the post-icteric period.

These observations open up a line of inquiry which might well be pursued further.

JAUNDICE

Recent work on the pathology of jaundice has shown that most cases fall fairly clearly into one of three main groups. These are—

1. Obstructive Jaundice: the result of a purely mechanical obstruction to the egress of bile, as for instance by a stone in the bile-duct, or by occlusion of the duct by carcinoma.
2. Toxic or Infective Jaundice: the result of injury to the liver-cells by a toxaemia: the jaundice occurring in some cases of septicaemia and pyaemia, in acute yellow atrophy, in poisoning by chloroform, phosphorus, and other drugs, in spirochaetosis, and many other conditions, belongs to this group. Catarrhal Jaundice appears to be a combination of Toxic with Obstructive Jaundice.
3. Haemolytic Jaundice: an 'extra-hepatic' jaundice, the result of excessive production of bilirubin from the break-down of haemoglobin by the reticulo-endothelial cells of spleen and liver, and not dependent on disease of the liver. Examples are Acholuric Familial Jaundice, Icterus Neonatorum, and the jaundice of Pernicious Anaemia.

By a consideration of clinical and laboratory information it is often not difficult to group a particular case of jaundice under one or other of these three heads. Catarrhal jaundice is an exception, for this may closely simulate the purely obstructive forms, and give considerable difficulty in diagnosis. In practice, however, most difficulty is encountered in the distinction between the various causes of obstructive and toxic jaundice, and here but little help is to be obtained from the laboratory.

The **pathological findings** in the three main groups of jaundice are as follows:

Obstructive Jaundice

The Bilirubin Content of the Blood

To the direct van den Bergh test a prompt positive reaction is always obtained. Such a result is suggestive of

a purely obstructive jaundice, though it may also be obtained in cases of catarrhal jaundice.

The Urine

Bile pigment and bile salts are present often in large amount. Urobilin or urobilinogen is usually absent; theoretically these substances will be found in the urine only when the bile-forming activity of the liver is impaired.

The Stools

The stools are clay-coloured; and in complete obstruction of the bile-duct, the chemical test for stercobilin is negative. A positive stercobilin test indicates incomplete obstruction.

Toxic Jaundice

The Bilirubin Content of the Blood

The results of the direct van den Bergh test are variable. Some cases may give a delayed reaction; others a prompt positive reaction, or more frequently a biphasic reaction.

The Urine

Bile pigment is present, usually in comparatively small amount. Urobilin or urobilinogen is present.

The Stools

The stools are often normally coloured, and the test for stercobilin is always positive.

Haemolytic Jaundice

The Bilirubin Content of the Blood

A delayed reaction is sometimes obtained with the direct van den Bergh test, but frequently the reaction is negative. The indirect van den Bergh reaction is always positive.

The Urine

Bile pigment is absent. Urobilin is often present.

The Stools

The colour of the stools is normal.

THE VAN DEN BERGH TEST

To appreciate the significance of the results of the van den Bergh reaction, it is necessary that a brief account be given of the nature of the test and of modern views on the pathology of jaundice. For fuller information the reader is referred to McNee's review of the subject (17).

The conversion of haemoglobin into bilirubin is effected by cells of the reticulo-endothelial system in the spleen and liver, and possibly in other situations. These cells in the liver are the Küpffer cells, flat branched cells lining the capillaries. The bilirubin thus formed passes through the liver-cells to reach the bile canaliculi. Bilirubin before passage through the liver-cells differs from that found in the bile, in that it is in combination with protein.

Van den Bergh made use of the diazo reagent of Ehrlich for the detection of bilirubin, applying it to the study of the blood-serum in cases of jaundice. **The direct van den Bergh test** consists in adding to 1 c.cm. of serum 0·25 c.cm. of freshly prepared diazo reagent. One of four things may happen with serum from a case of jaundice—

1. A bluish-violet colour appears immediately, and is maximal in ten to thirty seconds. This is a **prompt Positive Direct reaction,** and is given by sera from cases of obstructive jaundice, such as that caused by gall-stones. Bile also gives the prompt reaction, and this is therefore a test for bilirubin which has passed through liver-cells and is free from protein.
2. A reddish colour appears after one to fifteen minutes or longer, and gradually becomes more violet. This is called the **Delayed reaction**: it is given by sera from cases of pernicious anaemia, acholuric jaundice, and icterus neonatorum; that is, cases already described under the group of haemolytic jaundice, in which there is no evidence of obstruction to the bile-ducts, and bilirubin is absent from the urine. It is due to the presence in the serum of bilirubin which has not passed through the liver-cells, bilirubin in combination with protein, and therefore

incapable of passing through a healthy kidney. This form of bilirubin may also be detected by the indirect van den Bergh test, to be described shortly.

3. The result may be entirely negative.

4. A reddish colour appears immediately, and with a varying rapidity becomes violet. This is the **Biphasic reaction** and is thought to be due to the presence of both forms of bilirubin in the serum. It is given by sera from cases of toxic jaundice, including many of catarrhal jaundice.

The Indirect van den Bergh test is carried out when the direct test gives a negative or a delayed reaction. It is also the method used in all cases for the quantitative estimation of bilirubin in the blood. 1 c.cm. of 96 per cent. alcohol is added to 0·5 c.cm. of serum; this precipitates proteins. After centrifugalization the clear supernatant fluid is removed. If addition of the diazo reagent to this fluid produces an immediate colour, the indirect test is positive.

The recognition of the existence of these two forms of bilirubin and the possibility of detecting them in the blood-serum has shed much light on the pathology of jaundice. In purely obstructive forms, bilirubin which has passed the liver-cells is unable to pass along the bile-ducts, and so finds its way back into the blood-stream. In the various forms of toxic jaundice the liver-cells are damaged, and are therefore unable to transmit the usual amount of bilirubin; thus some of the 'indirect' form of bilirubin remains in the blood-stream. Further, swelling of the liver-cells produces a partial obstruction to the bile canaliculi, and we have some return to the blood-stream of 'direct' bilirubin. Thus in most cases of toxic jaundice both forms of bilirubin are to be found in the serum. In some cases damage to the liver-cells predominates, in others obstruction to the bile passages.

In the haemolytic forms of jaundice the Küpffer cells and the reticulo-endothelial cells of the spleen are producing more 'indirect' bilirubin than can be passed through

the liver-cells; consequently some remains behind in the blood.

The amount of bilirubin in the serum can be measured by the quantitative test, in which the colour is compared with that of an artificial standard. It has been found that normal serum contains 0·2 to 0·5 of a unit of indirect bilirubin (1 unit = 1 part in 200,000). The test enables us to detect **latent jaundice,** that is, an increase in the bilirubin content of the serum which is insufficient to cause coloration of the skin, or to appear in the urine. With obstruction to the bile passages, the blood must contain four units before bilirubin appears in the urine. The van den Bergh reaction is therefore a useful liver function test, detecting deficiency in the biliary function of the liver before this is recognizable by clinical signs.

DIFFERENTIAL DIAGNOSIS BETWEEN CATARRHAL JAUNDICE, JAUNDICE DUE TO GALL-STONES, AND JAUNDICE DUE TO CARCINOMA OF THE HEAD OF THE PANCREAS

These three conditions often come up for consideration in the diagnosis of a case of jaundice. An opinion is usually based almost entirely on clinical evidence, and laboratory investigations afford little support. The van den Bergh reaction does not help, for catarrhal jaundice may be predominantly obstructive in type. Evidence of patency or occlusion of the pancreatic duct is however important, and may be sought in examination of the stools and of the duodenal contents. In the absence of pancreatic ferments the stools show an increase in the fat content from the normal of about 25 per cent. to as much as 80 per cent. of the dried faeces, and this increase is due to unsplit fat, which normally forms about 6 per cent. of the dried faeces. Muscle-fibres are found in abundance, as is undigested starch (see p. 212).

By means of the duodenal tube it is possible to obtain a specimen of the duodenal contents, which can be examined for trypsin, lipase, and amylase. Complete absence of these ferments is strongly suggestive of a growth.

SPIROCHAETOSIS ICTERO-HAEMORRHAGICA

This is a specific infection with a spirochaete, in which jaundice occurs about the fourth or fifth day of the illness, and which is sometimes associated with purpura and haemorrhages from the mucous membranes. It was first identified as a distinct disease process during the Great War. The spirochaete is one which infects rats, and these animals are probably responsible for outbreaks of the disease in man. The diagnosis is confirmed by the demonstration of the spirochaete, which is present in small numbers in the blood up to the seventh day of the illness, and in the urine after the tenth day. Direct demonstration is often possible, but injection of blood or of the urinary deposit into the peritoneal cavity of a guinea-pig produces the disease in this animal in from three to seven days. The spirochaete is present in large numbers in the blood of the animal, and can be demonstrated by examination of it by the dark-ground illumination microscope.

As regards the jaundice the pathological findings are those of the infective type.

ACUTE YELLOW ATROPHY OF THE LIVER

Many poisons have a pronounced effect on the liver-cell. They may result in extreme fatty degeneration of the liver, or in acute atrophy with much shrinkage of the whole organ. In acute yellow atrophy, jaundice and clinical symptoms of intoxication from inefficiency of the metabolic functions of the liver, embraced by the expression 'icterus gravis', are present. Pregnancy is an important cause, as also is syphilis. Poisoning by chloroform, phosphorus, arsenobenzol compounds, and other chemicals, usually results in extreme fatty degeneration of the liver, but icterus gravis may supervene, and in some cases the condition of the liver is one of acute yellow atrophy. In many cases the cause is not discoverable.

Pathological Findings

The Blood

The red count is normal and there is a moderate leucocytosis. The serum gives the biphasic reaction to the van den Bergh test.

The Urine

Bile pigment and urobilin are present. Albumin is present in small quantity. Casts, granular and epithelial, may be found. Leucin and tyrosin crystals may be found in the deposit; they are sometimes absent, and in any case are not pathognomonic of the condition. There is often an increase in the percentage of nitrogen excreted as ammonia, due to acidosis.

ACHOLURIC FAMILIAL JAUNDICE (See p. 129)

PORTAL CIRRHOSIS.

The common form of cirrhosis of the liver is the result of a slowly progressive destruction of liver-cells, followed by replacement fibrosis. The primary damage to the liver-cells results from unknown toxic substances absorbed from the alimentary tract, probably formed secondarily to chronic alcoholic gastro-enteritis in the majority of cases. A compensatory hypertrophy of liver tissue prevents, in all but a few cases, symptoms due to liver insufficiency.

Pathological Findings

The Blood

In the early stages the blood-count is usually normal, and is of little help in diagnosis. In advanced cases, especially when infective complications have occurred, there may be severe anaemia of the secondary type, with a mild degree of neutrophile leucocytosis.

Liver Function Tests

The tests described in a preceding section are frequently positive, though negative results to all of them are often obtained. Negative results are therefore of no diagnostic value. The prognostic value of the glycuronic acid reaction has been mentioned.

Jaundice

Clinical jaundice is usually absent, but 'latent jaundice' is demonstrated in a large proportion of cases (see p. 223).

The Urine

When clinical jaundice occurs, generally slight and transient, bile pigments and salts may appear in the urine.

The urine is often diminished in quantity, and of high specific gravity. Urobilin is usually present in pathological amount. In advanced cases the ammonia-nitrogen percentage is increased: this is a manifestation of acidosis. Albuminuria and casts are often present in late cases.

Gastric test meal: deficient secretion of hydrochloric acid is almost invariable.

Ascites

The ascitic fluid usually has the characters of a transudate. A chyloid effusion is sometimes found. Though frequently sterile, it is not uncommon for a coliform bacillus to be obtained on culture. In some cases the characters of the fluid are modified by the existence of a chronic peritonitis. The specific gravity of the fluid is then higher than 1,015, and polymorphonuclear leucocytes are found. If tuberculous peritonitis has supervened, a not uncommon complication, 50 per cent. or more of the cells of the fluid will be found to be lymphocytes (see p. 231).

HANOT'S CIRRHOSIS

(Hypertrophic Biliary Cirrhosis)

This is a rare chronic disease, which affects principally young adult males. There is enlargement of the liver and spleen, associated with persistent jaundice, subject to exacerbations and periodic febrile attacks. Ascites does not occur. The aetiology is unknown.

Pathological Findings

The Blood

There is usually a pronounced secondary anaemia. The leucocyte count may be within the normal limits, but frequently it is moderately increased.

Jaundice is a prominent feature of the disease, and is of the toxic or infective type. A biphasic van den Bergh

reaction may therefore be expected, but this is of little diagnostic value.

The Urine

Bile pigments and salts are present. Albumin and casts may be found.

The Stools are normally coloured.

SYPHILIS OF THE LIVER

Tertiary syphilis of the liver may simulate clinically a variety of other diseases of this organ. Differential diagnosis is made very largely on clinical observation, though in any obscure liver disorder the result of the Wassermann test is of great assistance. Taking all cases of tertiary syphilis, both treated and untreated, the percentage of positive Wassermann reactions is probably about eighty-five. There is usually a secondary anaemia, very variable in degree. Fever may be present.

HYDATID DISEASE OF THE LIVER

A hydatid cyst of the liver has usually to be differentiated from a new growth and a gumma.

The Pathological Findings of most help in diagnosis are:

I. Eosinophilia.
II. A Negative Wassermann Reaction.
III. A Positive Hydatid Complement Fixation Test (see p. 182).
IV. A Positive Intradermal Reaction (see p. 180).

MALIGNANT GROWTHS IN THE LIVER

Carcinoma is the commonest form of new growth in the liver; occasionally it is primary, but the great majority are secondary. The primary tumour may affect almost any organ; its most common sites are the stomach, the colon, pancreas, gall-bladder, breast, and uterus. The pathological findings will be those of cancer in general, together with evidence of liver insufficiency. Clinical jaundice occurs in 50 to 60 per cent. of cases. The findings peculiar to cancer

of the stomach (p. 165) and cancer of the pancreas (p. 213) are considered separately.

Pathological Findings in Cancer

The Blood

There is an anaemia of the secondary type. The degree of this varies with the stage of the disease, the site of the primary growth, and no doubt with other factors. It is commonly pronounced in cancer of the liver. Simon finds that normoblasts occur in a large percentage of cases, frequently before the anaemia is severe. The leucocytes may be increased or normal. An eosinophilia may occur.

SUPPURATIVE PYLEPHLEBITIS

This condition is invariably secondary to an acute primary infective focus within the abdomen, most commonly an acute appendicitis. The diagnosis, if made at all, is made largely on clinical grounds.

The Pathological Findings are these :

The Blood

A secondary anaemia probably exists before liver involvement, but in any case becomes marked with the progress of the infection. The leucocytes are considerably increased, figures between 20,000 and 50,000 per c.mm. being commonly obtained. Blood-culture is usually sterile. Bilirubin is usually demonstrable in the serum. (Clinical jaundice occurs in about 50 per cent. of cases.)

A right pleural effusion is a fairly common complication. The fluid has the characters of an exudate, in which polymorphonuclear leucocytes predominate.

GALL-STONES

Jaundice due to gall-stones has been discussed (see p. 223).

The Blood

Gall-stones do not necessarily cause any alteration in the blood-count, whether their nature be metabolic or inflammatory. (In chronic cholecystitis the leucocyte count is commonly normal.)

Plasma Cholesterol

Sir Berkeley Moynihan (18) gives the following figures: the 'normal' cholesterol content is from 0·13 to 0·16 per cent.; from 0·16 to 0·19 per cent. is regarded as hypercholesterolaemia. Of a series of cases of cholelithiasis 23 per cent. showed high normal figures, 65 per cent. hypercholesterolaemia, and 11·5 per cent. had normal values.

In gastric ulcer 23 per cent., and in duodenal ulcer 12·2 per cent., had hypercholesterolaemia.

Thus it can be said that a patient with gall-stones will probably show hypercholesterolaemia. A patient with peptic ulcer, in the absence of arteriosclerosis, chronic nephritis, diabetes, and pregnancy, will probably not show hypercholesterolaemia.

As probability is frequently the guiding principle in diagnosis, these facts may be of value.

CHOLECYSTITIS

Chronic cholecystitis has been discussed (see p. 93). Acute cholecystitis may be catarrhal or suppurative. Acute catarrhal cholecystitis commonly becomes chronic, and may lead to a chronic accumulation of pus in the gall-bladder.

In acute suppurative cholecystitis the leucocyte count may be of assistance in diagnosis: there is a marked increase in the polymorphonuclears, the average total count being from 20,000 to 30,000 per c.mm. The symptoms, however, are such as to indicate immediate laparotomy. Jaundice does not occur, unless cholangitis develops; this is a rare complication.

In the acute catarrhal form help may be obtained from examination of the blood and of the bile obtained by the duodenal tube.

The Blood

The red cell count and haemoglobin are probably normal at the onset of the infection; some anaemia develops later. The leucocyte count shows a moderate increase in the polymorphonuclear cells; this returns to normal as the disease becomes chronic.

The Bile

The method of obtaining specimens is described on p. 94. The bile contains polymorphonuclear leucocytes and the infecting organism may be isolated by culture. *B. coli*, *Staphylococcus aureus*, and streptococci are the organisms most commonly encountered. *B. typhosus* and *B. paratyphosus* are occasionally found.

CHAPTER XVII

DISEASES OF THE PERITONEUM

PERITONITIS

THERE are three main types of acute peritonitis. In order of frequency they are: septic peritonitis, tuberculous peritonitis, pneumococcal peritonitis.

Clinical pathology will give certain information regarding both diagnosis and prognosis in these conditions.

SEPTIC PERITONITIS (not pneumococcal) is generally secondary to some lesion of an abdominal organ, and may be localized or general. Acute appendicitis, ruptured or leaking gastric or duodenal ulcer, and acute cholecystitis are the commonest causes.

A leucopenia or a normal white blood count is not found in acute peritonitis unless the infection is peculiarly fulminant. Comparison between the total and differential counts, as in appendicitis, will give useful information as to the severity of the lesion. A leucocytosis of some degree is generally present, the figure usually being above 15,000. The degree of leucocytosis is in some measure proportional to the severity of the infection, and a series of counts in a suspected case may give information as to the development of a peritoneal lesion.

TUBERCULOUS PERITONITIS in its onset is sometimes so sudden as to simulate clinically an appendicitis.

In this case there may be an associated polymorphonuclear leucocytosis; but this is not as a rule accompanied by that decrease in the total eosinophile count usual in pyogenic conditions. A leucopenia is frequent, more especially in adults. The absence of a leucocytosis, particularly if the eosinophile count be normal, is in favour of the diagnosis of tuberculous peritonitis. There is also frequently present a leucocytosis, due largely to an absolute increase in the number of lymphocytes.

The ascitic fluid from a case of tuberculous peritonitis has the following characteristics: The colour is yellowish,

occasionally with a greenish tint, or, in an acute case, may be red from contained blood. A clot forms, except in the specimen collected for cytological examination in an oxalated tube.

The specific gravity is above 1,015. The albumin percentage is above 3.

Cytological examination shows the presence of lymphocytes, a few polymorphonuclears, and occasional endothelial cells in proportions which vary, but which are generally about 70 per cent., 25 per cent., and 5 per cent. respectively. Red blood-cells may be found. The more acute the onset the higher is the proportion of polymorphonuclears, but with the development of chronicity the polymorphonuclear content falls. The tubercle bacillus is not usually detectable. Its presence may occasionally be demonstrable by animal inoculation.

Pneumococcal Peritonitis is occasionally primary, especially in children; and under those circumstances it presents pathological findings of its own. The chief are leucocytosis, the presence of pneumococci in the peritoneal fluid, and a positive blood-culture.

A leucocytosis is almost invariable, except in very fulminating cases; pneumococci can be found in fluid obtained from an exploratory paracentesis abdominis, and their presence may be diagnostic. Films to prove the presence of capsules, as well as cultures, are very desirable; a positive blood culture generally indicates a fatal issue. The importance of obtaining the pneumococcus and of determining its type is great, for immediate operation is contra-indicated, and valuable help can be obtained from serum treatment. Autogenous vaccines in suitably small doses may be tried. Surgical treatment is generally necessary later in most cases.

ASCITIC FLUID

The commoner causes of ascites are inflammations of the peritoneum, transudation of fluid into the peritoneal cavity as in cardiac and renal disease, the possibly combined effect in cirrhosis of the liver, and the presence of new growth nodules.

Ascitic fluid for diagnostic purposes should be withdrawn into two receptacles of easily portable size. The first is a plain sterile vessel; the second is similar, but contains potassium oxalate crystals to prevent coagulation, and thus to allow of a more efficient cytological examination.

In examining ascitic fluid the following characteristics may give information of value: the colour, the presence of clot, the specific gravity, the protein content, the cytology, and the bacteriology.

Colour

A clear fluid is sometimes found in transudates. A yellow, green, or yellowish-green colour is found in both transudates and exudates, and as a rule the fluid is opalescent or semi-translucent. An opaque milky appearance is found in chylous and in pseudo-chylous ascites. The former condition is due to the presence of true chyle resulting from trauma to or obstruction of the cisterna chyli or its duct, the commonest cause being malignant disease. Pseudo-chylous ascites occurs also in some cases of malignant disease, in peritoneal tuberculosis, certain hepatic diseases, puerperal sepsis, lymphadenoma, cirrhosis of the liver, and occasionally in cardiovascular disease. The distinctive points in differentiating the two are: chylous fluid contains very few cells but much emulsified fat (about 3 per cent.) and granular debris; pseudo-chylous fluid contains many endothelial cells, mostly degenerate, and less fat. The pseudo-chylous fluids are of two types, and can be referred to as chyloid and chyliform.

In the former, the milkiness is due to fat globules which are thought to have their origin in fatty degeneration of the endothelial cells. In the latter, it is the result of the presence of a substance of a protein-like nature.

Blood is frequently present in ascitic fluid. Generally, the quantity is small, as in the more acute type of tuberculous peritonitis, and is only discoverable by the microscopic recognition of erythrocytes. Occasionally, there is enough to colour the fluid red. Sometimes nearly pure blood is present. The less common causes of this are trauma or

rupture of a viscus, torsion and extreme congestion of some organ such as a cystic ovary, extra-uterine gestation, acute tuberculous peritonitis, and occasionally cirrhosis of the liver. The most frequent cause of a blood-stained effusion is new growth affecting the peritoneum.

Clotting is present in exudates, particularly in tuberculous peritonitis and in other chronic inflammatory conditions, and also in carcinoma, but absent in the transudates of heart failure and nephritis. Clotting may or may not be present in cirrhosis of the liver.

The specific gravity is below 1,015 in transudates, but over 1,018 in inflammatory exudates and in carcinoma. In cirrhosis of the liver an intermediate figure sometimes occurs.

The protein content is below 3 per cent. in transudates, and above 3 per cent. in exudates and in carcinoma. In cirrhosis the figure is often intermediate between the two groups.

Cells

The cytology of the fluid in tuberculous peritonitis has been dealt with above.

In cirrhosis of the liver the cells are few in number, and are chiefly flat endothelial cells, but a few lymphocytes also occur. In carcinoma the cells are numerous, most of them being endothelial cells, and a few being lymphocytes; occasionally, the presence of masses or groups of cubical cells showing mitotic figures will give a clue to the diagnosis, and more rarely an actual minute tumour mass is found, in the withdrawn fluid or in the needle lumen, whose cytology is diagnostic.

Bacteria

The tubercle bacillus is practically never demonstrable in ascitic fluid. If, however, a large quantity is collected in vessels containing oxalate or citrate and allowed to stand, injection of the centrifugalized deposit into guinea-pigs is followed by a positive result in a small percentage of cases. Alternatively, the clot can be digested with antiformin and the centrifugalized deposit similarly injected.

In 'septic' peritonitis the organism is always to be found in the fluid. In pneumococcal peritonitis the 'fluid' is generally sero-fibrinous, and the clinical condition frequently hardly merits the label 'ascites'; the pneumococcus is always to be found.

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E. DISEASES OF THE RESPIRATORY SYSTEM

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CHAPTER XVIII

EXAMINATION OF THE SPUTUM

Pathological evidence regarding disease of the respiratory organs can be gathered under two heads. Firstly, there is the reaction of the tract, regarding it as a surface organ, to the infection or disease. Secondly, there are the changes found in the blood or in other distant constituents of the body. The best indicator of the former is the sputum.

THE SPUTUM

The sputum should be sent in as fresh a condition as possible to the laboratory. A special journey is often worth while. Exposure to severe cold should be avoided.

General Considerations

Normally there is no sputum. Any form of irritation will stimulate the mucous glands to secrete mucus as a protective mechanism. This enmeshes the irritating factors, bacterial or otherwise, and bears them to the mouth. Where the foreign body is merely a dead particle of dust the process goes no farther, but when by chemical or other means the bronchial mucosa is injured or irritated, there are added to the sputum evidences of local damage and inflammation. Generally, these correspond accurately with the type of inflammation or with the particular stage the process has reached.

The first stage in an inflammatory process affecting a hollow viscus is hyperaemia. The next is the outpouring of a mixture of mucus and of serum in proportions varying greatly with the viscus and the disease. Should the local hyperaemia be considerable, or should the mucosa be sufficiently injured, red blood-cells will also be extruded in greater or in smaller numbers. These may remain uninjured or may become lysed or changed by local conditions. Later there is, in addition to the outpouring of mucus, a diapedesis of phagocytes into the lumen. To make the

local picture a complete one it is necessary to add the cause of the inflammation. If this is an organism it will at first spread and be found in culture; later, unless the condition progresses to a fatal issue, it will become fewer in numbers and will die off. Alternatively, other organisms will take advantage of the ground it has won and will appear as secondary invaders with it. In such cases the original germ may persist with the later arrivals or may die out.

Sputum arises also, primarily or secondarily, from lung tissue. Mechanical interference with this, or inflammatory disease of it, will produce sputum. Examples of the former are infarction or acute oedema of the lung, and of the latter pneumonia and phthisis.

Evidence that lung tissue has been damaged can be deduced from two findings, the presence of elastic fibres, and the presence of a definite quantity of albumin in the sputum. There are certain characteristics of the sputum that are worthy of note.

MACROSCOPICAL CHARACTERISTICS

Quantity

Black-coloured sputum in town dwellers indicates that the sputum is small in total amount, for the soot in a large quantity of inhaled air is concentrated into a small volume of sputum. Large quantities of sputum are found in acute oedema of the lungs, pituitous bronchitis, acute bronchiolectasis, abscess, gangrene, phthisis with much cavitation, and in the spitting up of an empyema.

The sputum of acute oedema of the lungs is abundant, often pink, frothy, containing a considerable quantity of albumin, and is frequently tinged with blood. That of pituitous catarrh is colourless, frothy above, but fluid and watery below, and not containing albumin.

Reaction

Fresh sputum is alkaline in reaction. That which has been static in a cavity or in a sputum cup for some length of time may, as a result of fermentation, be acid.

Colour

Intimate and homogeneous staining of sputum with blood, apart from gross haemoptysis, indicates as a rule bleeding lung parenchyma, as in tuberculosis, influenzal pneumonia, neoplasm of the lung, infarction, or congestion due to mitral stenosis. Red streaks in muco-purulent sputum indicate chronic bronchitis and sometimes tuberculosis. Definite clots of blood mixed intimately with sputum suggest bleeding from a pulmonary vessel, as in tuberculosis, and aneurysm. Pure blood may be coughed up in all of the above conditions, except in chronic bronchitis, and also in bronchiectasis. The pink sputum of acute oedema of the lungs is characteristic.

Brown colour in a sputum suggests changed blood, as in lobar pneumonia; or in rare cases the contents of an amoebic liver abscess that has pointed upwards. Dark brown sputum, 'prune juice', is present in certain severe and generally fatal cases of pneumonia. Brown sputum is sometimes found in infarction.

A green colour is often found in cases of jaundice, caseous pneumonia, and in a slowly resolving lobar pneumonia.

A yellow sputum is often found in chronic bronchitis and in phthisis.

The colour here is due to the high pus content.

Consistency

A frothy sputum is indicative of considerable and partially ineffective coughing efforts, for air has been repeatedly driven through the sputum *in situ* with the effect of 'whipping it up' well without dislodging it.

A sputum may be wholly or partially tenacious; that of lobar pneumonia, acute bronchitis, and bronchial asthma belongs to the former category. Pneumonic sputum even adheres at times to the bottom of the inverted cup. Most sputa contain masses that are themselves tenacious units. The least tenacious and most fluid sputa are found in acute oedema of the lungs and in pituitous catarrh.

According to the degree of admixture of its serous or fibrinous fractions a sputum will separate into layers or

remain homogeneous. Layer formation is present especially in bronchiectasis, acute and chronic, and in gangrene. There are two layers, fluid above and muco-purulent below; or three, froth, fluid, and muco-pus, according to the effectiveness of the cough. Layer formation is also sometimes found in cases of phthisis with considerable cavitation.

Shape

Certain shapes assumed by the sputa indicate pathological or physical conditions. Nummulation, or the presence of flat, circular, coin-shaped masses of muco-pus, is said to be found chiefly in cases of phthisis with cavitation.

Fibrinous casts of portions of the bronchial tree are characteristic of fibrinous bronchitis (generally a pneumococcal condition) and of diphtheria.

Blood-clot casts are occasionally found, generally post mortem, after extensive haemoptysis.

Calcareous portions, generally from lymphatic glands that have sloughed through the bronchial wall, are occasionally coughed up. They, of course, indicate old tuberculous disease. Broncholiths which result from deposition of lime salts, in or near the bronchial wall, are sometimes found. They are most frequently associated with chronic tuberculosis.

Smell

Sputum is generally odourless. That of bronchiectasis sooner or later becomes unpleasantly offensive. The sputum also has an odour in gangrene, abscess and necrosis of the lung, in a coughed-up empyema, and sometimes in tuberculosis and chronic bronchitis. The unpleasant smell is often associated with the presence of anaerobic organisms; and local conditions favouring their growth, such as cavitation or retention of bronchial secretion, are to be sought for under the circumstances.

MICROSCOPIC CHARACTERISTICS

Red Blood-cells

Red blood-cells may easily enter the sputum from the naso-pharynx and gums. If, however, the sputum has been collected conscientiously by the nurse or patient, and is the

product of a true coughing effort, blood in it assumes considerable significance. In addition to the conditions in which considerable naked-eye blood is present, there are found, in severe cardiac congestion of the lungs, cells of the pulmonary alveoli, which have ingested some of the numerous red blood corpuscles that have escaped from the capillaries. These 'Herzfehlerzellen' also are sometimes seen after infarction or a haemoptysis.

White Blood-cells

The only white cell whose presence in sputum is helpful is the eosinophile. It suggests true spasmodic asthma, or in rarer cases sensitivity against the organism present. It should be borne in mind that the presence of a few squamous epithelial cells suggests contamination with saliva: the presence of many suggests a completely oral or pharyngeal origin. It is impossible to draw sound conclusions regarding diagnosis or prognosis from the relative proportions of polymorphonuclear cells and lymphocytes found.

Epithelioid Cells

The presence of clusters of polygonal, frequently multinuclear, cells with well-stained nuclei is suggestive of pulmonary neoplasm.

Elastic Fibres

Before the discovery of the tubercle bacillus the presence of elastic fibres was the best laboratory evidence for tuberculosis. In 90 per cent. of cases where they are found pulmonary tuberculosis is present. Pathologically they indicate destruction of alveolar tissue. Rarer conditions where this occurs are pulmonary abscess and gangrene. Their presence should be sought more frequently in cases of doubt.

Animal Parasites

The presence of hooklets or fragments of the wall of daughter cysts is sometimes the only means of diagnosing echinococcus disease of the lung. There is in such cases as a rule also an eosinophilia of the blood, and Casoni's reaction is positive (see p. 180).

Bacteria

There are two generalizations of value to be made with regard to the bacteriological examination of sputum. The first is that tubercle bacilli may be found in the first specimens coughed up in the morning when they are not to be found later. The second is that a film of sputum will give a much truer picture of the bacteriology than will a culture. There are two reasons for this: the secondary invaders are often more vigorous growers; the media used cannot help being largely selective. The pathologist who is asked to provide a vaccine for the treatment of some respiratory infection should therefore be given the sputum fresh and whole, not an agar-slope stroked haphazard by a keen amateur. An additional safeguard in collecting sputum for bacteriological examination is to wash the lump or lumps well in cool boiled water, to withdraw them with sterile forceps, and to send them in a sterile pot to the pathologist.

Crystals

Fatty acid, cholesterol, leucin, tyrosin, triple phosphate, and calcium oxalate crystals have all been found in putrid sputum. Bronchiectasis, putrid bronchitis, abscess, gangrene, and occasionally tuberculosis are the conditions that may give rise to them. Charcot-Leyden crystals are present chiefly in asthma.

CHEMICAL EXAMINATION OF SPUTUM

A large quantity of albumin is found in the sputum in pneumonia, pulmonary oedema, and perforating empyema. The significance of smaller quantities is not so clear. Although it is true that in most cases of chronic bronchitis there is no albumin, or only the faintest trace, and that in many cases of pulmonary tuberculosis a measurable quantity is present, yet it is also certain that pulmonary tuberculosis may produce sputum containing no albumin, and that occasionally chronic bronchitis, tuberculosis being quite unproven, may produce a sputum containing a definite quantity.

CHAPTER XIX

DISEASES OF THE LUNGS AND BRONCHI

ACUTE BRONCHITIS

Acute bronchitis may be primary or secondary.

Secondary Acute Bronchitis may follow measles, influenza, typhoid, pertussis, syphilis, and certain much rarer conditions. In every case the sputum is a carrier of the infective agent; typhoid bacilli, for instance, may be present in pure culture.

In the early stages of the first three diseases there is a leucopenia; in measles this persists in the absence of complications; the same is true of influenza for the first four or five days, after which the count rises to about the normal figure. In influenzal pneumonia, where the causative organism is *B. influenzae* of Pfeiffer, the white count is frequently within the region of 12,000 as opposed to the 25,000 or more of pneumococcal pneumonia. But even here an empyema or other pyogenic complication is associated with the usual degree of leucocytosis. The secondary bronchitides tend to be more catarrhal and less mucoid during their period of onset than simple acute bronchitis.

The organisms chiefly responsible for Primary Acute Bronchitis are the pneumococcus, *B. influenzae*, *Micrococcus catarrhalis*, *B. coryzae segmentosus*, streptococci, and staphylococci.

Sputum

During the first two days the sputum is either absent or very scanty. When present it is tenacious, semi-transparent, and composed of a matrix of mucin in which are embedded a few bronchial epithelial cells, with occasional mononuclear and red or white blood-cells. The causative organisms are to be found during this stage in practically pure culture.

After the first two days the sputum becomes more fluid, and microscopically the white blood-cells are increased in number. Later, from 5 to 15 days from the onset, according

to the severity of the attack and the resistance of the patient, the sputum becomes greatly increased in amount, considerably less tenacious and containing a far larger number of polymorphonuclear cells, sometimes to the extent of being almost pure pus, the colour becoming yellow or yellowish green. The organisms by now may still be in pure culture, but are frequently accompanied by an even greater number of secondary invaders.

Finally, an increase in fluidity coincides with a diminution and disappearance of the sputum.

The sputum at any stage may be streaked with small quantities of bright red blood.

Blood

If the causative organism is Pfeiffer's bacillus there is usually to begin with a leucopenia. In the other infections a slight leucocytosis is common. Serial white blood counts in small children and in old people, in whom the disease is more dangerous, may show an increase in the white count with the onset of a secondary broncho-pneumonia, tonsillitis, or otitis media.

Vaccine treatment is of little value in acute bronchitis.

CHRONIC BRONCHITIS

This heading covers several varieties. There is a large group in which a chronic infection of the upper air-passages, nasal sinuses, tonsils, or mouth, appears to be the primary focus. From this is originated a periodic secondary invasion of the bronchial tree. Treatment of the primary focus will be followed by a disappearance of the bronchitis. In this connexion it is important to remember that pulmonary tuberculosis is not infrequently associated with such a secondary infection, and that the finding of tubercle bacilli does not excuse the physician for neglect in treating septic tonsils.

Sputum

This secondary form of chronic bronchitis is usually manifested by a fairly abundant muco-purulent sputum, often

most in quantity in the morning. Microscopically it contains many pus cells and a variety of organisms, amongst which it may be difficult to detect the original culprit. A film is likely to give a better clue to this than is a direct culture. The former may show a very large predominance of Pfeiffer's bacillus, which in the culture may be crowded out by vigorous staphylococci. The organisms most frequently found are those referred to under acute bronchitis.

A second common variety of chronic bronchitis is that associated with emphysema. Here the sputum is scanty and often absent. An occasional tenacious, colourless, mucoid lump may be spat up in the morning. Microscopical examination here will give little help.

If nasal and oral foci are not left untreated, the vaccine treatment of chronic bronchitis, if properly carried out, is not infrequently successful. A specimen of freshly coughed up sputum (as free from oral contamination as possible) is sent with all speed to the pathologist, who makes a film and then cultures the specimen. If the film of the original material contains a pure growth of some organism or a great preponderance of it, an attempt is made to isolate this and to make an emulsion. Otherwise the vaccine is made in as close an imitation of the original picture as possible.

Blood

The red blood count is of considerable value in certain types of chronic bronchitis and emphysema. A count of six millions suggests a severe impediment to full oxygenation, and a progressive rise from above this figure is of serious import. A figure of over seven millions generally indicates a duration of life limited to months only.

FIBRINOUS BRONCHITIS

The chief clinical characteristic of this disease is the coughing up periodically of somewhat tenacious fibrinous casts of some of the larger bronchi. The diagnosis or prognosis does not depend upon pathological findings, though it must be remembered that diphtheritic bronchial casts, less

tenacious and containing the Klebs-Löffler bacillus, may sometimes occur in diphtheria. The organism most frequently found is the pneumococcus. Vaccine treatment, in view of the chronicity of the disease, may be worth a trial, provided that no naso-pharyngeal focus is present.

BRONCHIECTASIS

Sputum

By the time that bronchiectasis is well established the retained secretion is always heavily infected by a large number of different organisms. Bacteriological examination of the sputum is therefore usually of no help. Occasionally, however, cases clinically resembling bronchiectasis or abscess of the lung are found where the sputum contains large numbers of spirilla and fusiform bacilli. These are not to be cultivated in ordinary media, and will therefore be missed completely unless films of carefully collected sputum are made direct. Diagnosis is important, for treatment by neokharsivan or some similar arsenical drug is often followed by strikingly successful results. Tuberculous disease is sometimes found in conjunction with what is clinically termed bronchiectasis. Discovery of the tubercle bacillus in the sputum is therefore an important point in prognosis.

The Blood-count

The pyogenic nature of the disease is reflected, proportionately to the degree of retention of pus, in the white blood count. There is as a rule some **leucocytosis** (10,000–15,000), but this is increased in two conditions, either as a result of temporarily deficient bronchial drainage, or as a result of the onset of a secondary broncho-pneumonia. Thus fever with an increased leucocytosis in a case of bronchiectasis is a suggestive phenomenon. A rare third possibility in these circumstances is cerebral abscess.

The presence of a secondary **anaemia,** generally of the chlorotic type, is of use as an indication of the amount of toxaemia. Repeated haemoglobin estimations are of value in following and estimating the progress of the disease.

In very chronic cases, with little or no toxaemia, there may be a compensatory increase in the number of red blood-cells.

INFLUENZA

Influenza is probably a generalized infection. It is placed under the heading of respiratory diseases here because the aetiological agent is unknown, and because its main signs and symptoms are those of an acute infection of the respiratory tract.

The apparent course followed by the pathology of the disease is as follows: Infection is generally air-borne and the patient is attacked suddenly by headache, prostration, and pain in the back and limbs, and frequently tracheitis, pharyngitis, or other upper respiratory inflammatory condition. During this stage, that of congestion and hyperaemia of the respiratory tree, there is no constantly recoverable organism to which blame can be attached.

After a few days, however, sputum begins to be coughed up and an acute bronchitis develops. This not infrequently is followed by a definite broncho-pneumonia. In the sputum Pfeiffer's bacillus is in many instances demonstrable, often in association with some other organism such as the pneumococcus, staphylococcus, streptococcus, or *Micrococcus catarrhalis*, or these organisms may be present in pure culture. The presumption is that the disease is caused by some unknown agent, possibly a filter-passer, and that advantage is taken of the patient's lowered resistance by any pathogenic organism that happens to be present. When a pneumonia develops it may be one caused by Pfeiffer's bacillus, or by one of the other associated invaders, or indeed by a combination of two or more.

Pathological Findings

Blood

The haemoglobin and red cell figures are unaltered. There is usually a definite leucopenia. This is present soon after the onset of the disease and persists for a number of days. Should pneumonia supervene, the leucopenia may

persist, or more commonly give place to a slight leucocytosis (10,000–15,000), instead of the higher figures usually found in other types of pneumonia. If in such a case the leucocyte count rises considerably during the pneumonia or towards the end of its course, the presence of an empyema or some other pyogenic complication should be suspected. Acute middle-ear and sinus infection are common.

Sputum

An examination of the sputum, cleanly and carefully collected, is of value in an influenzal broncho-pneumonia. Smears as well as cultures should be taken, and the former are likely to give the clearer picture of the bacteriological flora.

Haemoptysis is common, and, since the type of tissue affected is the same as in phthisis, the macroscopical appearance of the bloody sputum is frequently similar in both conditions. The colour is seldom rusty in influenzal broncho-pneumonia, though it may be so in the lobar type of the disease.

The type of organism present should be taken into account in estimating prognosis. A broncho-pneumonia caused by a pure Pfeiffer's bacillus infection, or by a combination of this with *Micrococcus catarrhalis*, is of a less severe significance than is one caused by a haemolytic streptococcus or a pneumococcus, either pure or in association with Pfeiffer's bacillus.

Vaccine treatment has not proved of value in influenza.

PERTUSSIS

The infectious agent in whooping-cough is the bacillus of Bordet and Gengou. The organism is present in the respiratory secretion of carriers as well as in that of patients.

Children suffering from pertussis are not infrequently attacked by influenza, diphtheria, and broncho-pneumonia; moreover, the disease is apt to light up a quiescent tuberculosis which is miliary, pulmonary, or abdominal in type.

Pathological Findings

The commoner clinical pathological findings are those:

I. Of the Sputum.
II. Of the Blood.
III. Of the Cerebro-spinal Fluid.

The sputum in the first week of the disease contains the organism in very large numbers, sometimes in pure culture. In the second week their diminution begins, and this by the end of the fourth, or even earlier, is frequently complete, even though the whoop and other signs and symptoms persist. The organism is not found in the blood-stream.

The blood shows certain characteristic changes in the leucocyte count. A lymphocytosis is common, and is said to be best marked when the paroxysms are most frequent and most severe (1). The writer (2) has recorded a case where the total white count was 176,000 and the total lymphocyte count 116,000.

When pneumonia coexists the polymorphonuclear cells tend to predominate.

An anaemia does not usually occur.

The cerebro-spinal fluid is normal, or, if the convulsions are frequent, contains an excess of lymphocytes and of the reducing substances. Tuberculous and septic meningitis may both occur.

Treatment

Prophylactic vaccine treatment is of use. The doses should be large—500, 1,000, and 2,000 millions, the latter dose being given twice—and the intervals between the injections can be as short as two days, provided no febrile or undue local reaction occurs.

Reports as to the use of vaccine treatment therapeutically differ. It would seem that whereas it may be useful in the pre-paroxysmal stage, it is useless later in the disease.

PULMONARY TUBERCULOSIS

The original lesion in pulmonary tuberculosis is situated in the lung parenchyma. By the time that it has reached a size sufficient to produce symptoms it is in intimate con-

tact with the bronchial tree on the one hand, and with the blood-stream on the other. Pathological findings will therefore be due either to the absorption into the blood-stream of the tuberculous toxin, or to the ulcerative and inflammatory lesions of the finer bronchi.

To begin with, the **sputum** is absent or of small amount, but later there is often a considerable quantity. In the earliest cases, when correct diagnosis is difficult and of greatest value, it is sometimes necessary to persuade the patient to cough up phlegm by providing the suggestive influence of a sputum pot. Frequently a little can be obtained upon waking up in the morning, when there is none later in the day. The precautions hitherto described should be taken in its collection. The most characteristic contents of tuberculous sputum are tubercle bacilli, elastic fibres, and albumin.

Tubercle bacilli are frequently present in very small numbers. In cases of doubt, sputum should be examined a number of times. They may appear in the twelfth specimen after eleven negative results. Two methods other than that of repetition may offer success in refractory cases, the antiformin method and guinea-pig inoculation. The former consists in digesting with antiformin the other less resistant solid constituents of the sputum. To make the best use of this concentration method, sputum collected during a twenty-four, forty-eight, or even seventy-two hour period should be sent to the pathologist. After concentration the bacilli are searched for in the usual manner.

A similar large amount should ideally be sent when guinea-pig inoculation is intended, for most pathologists prefer to inoculate a concentrated specimen.

In the face of repeated negative findings, should the clinical picture still suggest pulmonary tuberculosis, other rarer conditions such as neoplasm, lymphadenoma, bronchopulmonary syphilis, bronchitis secondary to sinus infection, aspergillosis or moniliosis, and finally actinomycosis, should be borne in mind. Diagnosis of the three latter conditions is only possible by finding the causative organisms in the sputum.

Elastic fibres indicate destruction of pulmonary tissue, and, since phthisis is by far the commonest cause of such destruction, their appearance is always suggestive. An inquiry as to their presence might more often accompany one regarding that of tubercle bacilli.

The significance of the presence of **albumin** has been dealt with under the heading of chemical examination of sputum. (The simplest manner of testing sputum for the presence of albumin is to dilute it with an equal quantity of water and to add acetic acid (3 per cent.), to filter off the mucoid precipitate, and to test the clear filtrate by one of the usual methods for the presence of albumin.)

Other constituents of importance found in the sputum are secondarily infecting organisms and blood. Should a certain organism be recovered repeatedly from carefully collected and washed sputum the use of a vaccine may be well worth a trial.

With regard to the presence of blood, it should be remembered that blood-stained fluid may not infrequently be found staining the pillow in the morning in cases of pyorrhoea alveolaris. This, if collected, will be found to be saliva, and will contain many flat squamous cells, and not the polymorphonuclear cells characteristic of true sputum, tuberculous or otherwise. No information of value, as to the tuberculous nature of a sputum, can be gathered from a consideration as to what percentage of the constituent cells are lymphocytes or polymorphonuclears.

The Blood

The earlier stages of phthisis, especially in young women and girls, are frequently accompanied by an anaemia. This may affect the numbers of the red cells, but is frequently largely confined to the haemoglobin content, producing an anaemia of the chlorotic type. Indeed, chlorosis may be suspected before any thoracic signs develop. The later stages of the disease seem to be less frequently accompanied by an anaemia. This may be partly due to the fact that the blood is more concentrated as a whole in these patients.

The white cell count is usually normal. In the more acute cases a leucopenia, sometimes very considerable in extent, may occur, chiefly affecting the polymorphonuclear cells. The differential diagnosis as between acute tuberculosis and typhoid fever is thus made more difficult.

In the more chronic type a polymorphonuclear leucocytosis will accompany acute secondary infections by pyogenic organisms or such complications as acute pleurisy, meningitis, or ulceration of the intestines.

Arneth first enunciated the statement that the polymorphonuclear leucocytes in progressive tuberculosis tended to have fewer lobes to their nuclei than normal. Normally 5 per cent. possess one nucleus, 34 per cent. two, 42 per cent. three, 17 per cent. four, and 2 per cent. five. It appears to be fairly true that what he described as a shift to the left indicates an advance of the lesion, and to the right more successful resistance. Clinical data, however, are of greater value in estimating arrest or advance.

Examination of the blood, by concentration and guinea-pig inoculation, is of no value in diagnosis.

Urine

The urine may contain albumin if the patient is febrile. Tubercle bacilli may be found in the urine, by concentrating a twenty-four hour specimen, in cases of acute pulmonary tuberculosis, miliary or otherwise. Animal inoculation of the centrifugalized deposit may be necessary. A negative result does not exclude the condition.

Faeces

In children who swallow their sputum the stools should be repeatedly examined for the presence of the bacilli. Negative results are frequent, but with proper technique positive findings are sufficiently common to warrant the attempt in important cases.

TUBERCULIN

Tuberculin has been allotted two roles in the management of tuberculous patients, therapeutic and diagnostic.

The value of both has been much exaggerated. Thera-

peutically the majority of physicians hold that the dangers outweigh any possible benefit.

The diagnostic value of tuberculin depends upon the fact that the tissues of an animal, after infection by the bacillus, become, as a result of allergy, hypersensitive to some of its chemical constituents. With the presence of living bacilli in the body this hypersensitivity may last for many years without any sign of disease, for at least 90 per cent. of individuals become during the course of their life infected by the organism. In the great majority the infection is arrested in its earliest stages. In an adult, therefore, the presence of a positive tuberculin reaction has, with reference to any disease under consideration, no diagnostic value; in the case of the reaction being negative, provided the disease be not too acute, the diagnosis of active tuberculosis is unlikely.

In children below the age of ten a positive reaction is of increasing value with decrease in age, and a negative result is of considerable value.

It should be remembered that certain acute diseases, such as measles, pertussis, and influenza, render temporarily negative a reaction previously positive, even in the presence of active tuberculosis. Furthermore, acute miliary tuberculosis is often accompanied by a negative reaction.

The test is performed as follows:

The temperature is taken every two hours for two days preceding the test, in order to give a reliable control curve.

A subcutaneous injection of Koch's Old Tuberculin is then given, the first dose being 0·0001 gramme. Within twenty-four hours the reactions, if positive, should occur. They are three in type: local, general, and focal.

The local reaction consists of a definite reddening, frequently with some slight local induration, at the site of injection. The general reaction is manifested by rises in the temperature and pulse curves. The focal reaction may be shown by an increased output of sputum or by an increase in the physical signs over the suspected area of disease in the lungs.

Should no reactions occur, the second dose of 0·0005

gramme can be given after an interval of five days. A third dose of 0·001 gramme should follow in the face of persistent negative results, and in adults a fourth dose of 0·005 gramme may be given. It is safer to stop at this dose, and very unwise to give a dose larger than 0·01 gramme. When a reaction occurs, a second injection of the same dose is characteristically followed by a second reaction, equal to or of greater degree than the first.

Tuberculin should not be given to patients who have had fever within seven days. Its use is chiefly restricted to diagnosis in obscure chronic cases and in children.

Complement fixation has been used in the diagnosis of tuberculous disease. The exceedingly variable results obtained in the hands of many pathologists indicate that it is at present a method upon which reliance cannot be placed.

BRONCHO-PNEUMONIA

Broncho-pneumonia may be primary or secondary. In either case it is due to a definite pulmonary infection. The pathological findings will be caused on the one hand by toxic absorption from the diseased area, and on the other by the secretion from the secondary bronchitis.

Sputum

The causative organism of acute primary broncho-pneumonia is generally the pneumococcus. Those responsible for the secondary forms of the disease are pneumococci, streptococci, the *B. influenzae*, Friedländer's bacillus, *Micrococcus catarrhalis*, *B. typhosus*, *B. paratyphosus*, and several others.

It is important to obtain a clear idea as to the causative organism in broncho-pneumonia. In primary broncho-pneumonia the presence of a Type 1 pneumococcus may suggest the advisability of using Type 1 antiserum; in secondary broncho-pneumonias the discovery of a staphylococcus, or a streptococcus, or some other atypical organism, may suggest the pyogenic nature of the original condition.

Should the sputum contain elastic fibres there is evidence

of abscess formation or of lung destruction. In such cases the prognosis as to ultimate complete recovery of the lung should be guarded.

Blood

There is as a rule not much anaemia associated with broncho-pneumonia, unless the latter is a manifestation of septicaemia or of some other septic condition.

The white blood count as a rule is not so high in broncho-pneumonia as in lobar or croupous pneumonia. The figure is in most cases below 20,000. Increase in the count should be watched for, as it may indicate the development of an empyema.

Blood-culture is generally sterile.

Vaccine Treatment is as a rule of no value. In long-continued cases, provided that the same organism is repeatedly isolated in pure culture from sputum carefully collected, vaccine treatment is occasionally worth a trial. The dosage should be small, and should not produce an increase in the fever.

CHAPTER XX

DISEASES OF THE PLEURA

PLEURAL EFFUSIONS

General Considerations

The examination of pleural fluids yields knowledge directly as to the condition of the pleura and sometimes also of the adjacent lung. Pleural effusions can be classified under the headings of transudates and exudates. The former are the result of physical, and the latter of inflammatory causes.

The chief differences between the two types are: transudates produce no clot, whereas exudates frequently do; the specific gravity of transudates is as a rule lower than 1,014, that of exudates above 1,018; the percentage of albumin in transudates is usually below 1·5, that of exudates usually above 3. The cells in transudates are usually few in number, and in exudates more are found. Transudates generally contain epithelioid cells with a few lymphocytes; exudates contain lymphocytes, polymorphonuclears, eosinophiles, epithelioid cells, or new growth cells, according to the aetiological character of the fluid.

It is obvious that the presence of clot will seriously interfere with the accurate estimation of these physical, chemical, and cytological properties, and it is therefore advisable to place a few crystals of potassium oxalate in one of the receptacles in which the freshly withdrawn fluid is to be sent to the pathologist. Failure to do this will decrease the value of the evidence that can be obtained. Fluid withdrawn from empyemata frequently does not clot, though fibrinous flakes often coat their walls, and in them this precaution is unnecessary. Some of the fluid should always be placed in a sterile test-tube in addition, and this should be plugged with a sterile rubber cork or cap. Ordinary corks are practically unsterilizable.

The transudates found in the pleural cavity are present in heart failure and in hydraemic nephritis. They are light

yellow or light greenish in colour, and are sterile. Their physical characteristics have been described above.

The exudates found in the pleural cavity can be classified as serous, sero-fibrinous, purulent, haemorrhagic, putrid, and chylous. They have certain characteristics of colour, physical appearance, and smell.

Colour

The redness of certain effusions is due to blood. Bloody effusions are to be found in tuberculosis, trauma, neoplasm, aneurysm, cirrhosis of the liver, scurvy, purpuras, and other haemorrhagic states; also occasionally in pneumonia. A brownish colour suggests the presence of old bleeding, and is found in neoplastic conditions of the pleura. In case of doubt as to the nature of the brown colour in an effusion, a van den Bergh's test is of value in proving the presence of bilirubin, and thus of haemolysis. Clear or slightly opalescent pleural effusions of a greenish or yellowish colour are to be found in almost any condition except empyemata. The colour of empyemata varies from brownish yellow through yellow to green. The pneumococcal variety are as a rule of a greenish yellow colour, the streptococcal of a lighter yellow.

A lesion of the thoracic duct may in rare cases give rise to a milky effusion. A clear colourless fluid is found in hydatid disease.

Physical Consistency

Clot, in serous effusions, is most characteristic of a pleura irritated and inflamed by the tubercle bacillus. It is also to be found in neoplastic conditions, lymphadenoma, and acute rheumatism.

An acute empyema fluid on standing separates into two layers, a clearer upper and a more opaque lower portion; the more acute the empyema the larger is the upper more serous fraction.

Fragments of fibrin are characteristic of a less acute process, generally of a pneumococcal nature.

An established empyema is generally of a creamy consistency.

Smell

Serous pleural effusions are odourless. Pneumococcal and streptococcal empyemata have as a rule no smell. Should an empyema be offensive, causes other than a primary pneumonia must be considered. Above the diaphragm these are most commonly pyo-pneumothorax, septic infarct, actinomycosis, and bronchiectasis; abdominal conditions to be considered are perigastric sepsis, secondary to ulcer or carcinoma, or subdiaphragmatic abscess due to appendicular sepsis.

MICROSCOPICAL EXAMINATION

Cytology

The cytology of pleural effusions does not invariably give information capable of furnishing a dogmatic opinion. It is true, as a generalization, that the presence of a few cells of an endothelial nature suggests a transudate, that a lymphocytosis suggests tuberculosis, that a high polymorphonuclear count suggests some pyogenic infection.

It must be remembered, however, that at the onset of an acute tuberculous effusion a high percentage of polymorphonuclears, often of the order of 40 per cent., may occur. After the lapse of a few days this percentage falls, and by the end of a week there may be a very considerable reduction. In other cases there is a pure lymphocytosis from the outset. The higher the lymphocyte figure the greater is the likelihood of tuberculosis, and, conversely, the higher the polymorphonuclear percentage, the greater is the probability of some pyogenic infection. Moreover, the finding of a number of epithelial cells, even if they be multinuclear and in clumps, by no means proves the presence of a neoplasm; they may occur in syphilis or in other forms of chronic non-pyogenic irritation or inflammation. Definite new growth cells are of rare occurrence, and are never recognizable unless they happen to show mitosis.

Bacteriology

The bacteria most commonly found in purulent pleural effusions are pneumococci, streptococci, staphylococci, *B. influenzae*, *B. coli*, *B. typhosus*.

Sterility of an effusion by no means indicates that it is not of a pyogenic origin; many post-pneumonic and meta-pneumonic empyemata may be, or appear to be, sterile, owing to the death of a delicate organism in transit to the laboratory, or to the fact that it has actually died out *in situ*.

CLINICAL VARIETIES OF PLEURAL EFFUSION

Tuberculous Effusion

Tuberculous effusions may be haemorrhagic, serous, or opaque. The former may occur in miliary and in rapidly caseating pulmonary disease as well as in chronic phthisis. The serous effusions have been described above.

Tuberculous empyemata, so called, are not uncommon. They are generally associated with a rather diffuse caseous tuberculosis. The fluid is creamy, even oily in consistency, and of a yellowish white colour as a rule. Cytologically the cells are extremely degenerate and stain very poorly; there is much amorphous debris. The recognizable cells are chiefly lymphocytes with a few epithelial cells and polymorphonuclears. If ulceration has occurred red blood-cells will be present to a greater or less extent. Later the effusion may, as a result of a lesion of the thoracic duct, contain chyle.

Secondary infection of a tuberculous, serous, or empyematous effusion sometimes occurs. The organisms are most often streptococci, staphylococci, and pneumococci.

It is important to diagnose, if possible, the pure tuberculous empyemata; for resection of a rib in them may be followed by complete failure to heal, though in the secondarily infected cases it may be necessitated by circumstances. Pure tuberculous pleurisies are sterile. It is thus important to determine the cytology and bacteriology of all empyemata before surgical interference. The nature of all types of tuberculous effusion can be proved in a certain proportion of cases by guinea-pig inoculation. Fluid for this should be collected in a sterile manner and into a flask containing a few potassium oxalate crystals.

A pleural effusion in lymphadenoma may be indistinguishable in every respect from that of tuberculosis.

EMPYEMA

Pneumonic Empyema

Empyemata may accompany or follow lobar or lobular pneumonia. The organisms most often found are pneumococci and streptococci; others, such as Pfeiffer's bacillus and staphylococci, also occur.

Accompanying many cases of pneumonia is an excess of fluid in the pleural cavity. This is as a rule small in quantity, and the exploring syringe may not recover more than 5 c.cm. This is slightly opalescent, yellowish or greenish in tint, often partly coagulable and sterile. Microscopically it contains a few cells, mostly polymorphonuclears. As a rule these characteristics persist until resolution.

Should an actual infection of the pleura occur, the appearance of the empyema fluid varies with the stage of the process. In the acute stage the fluid is distinctly opalescent but not yet opaque; the colour is light yellow or green; no clot forms, and on standing there is separation into two layers. The cells are polymorphonuclears, and in most cases the causative organisms are seen in the film. The fluid may or may not be sterile on culture.

During this acute stage, especially if an active pneumonia coexists, it is wise to attempt treatment by aspiration. In many children and in fewer adults aspiration alone, sometimes repeated twice or thrice, will be followed by resolution. Should the fluid become more opaque, should organisms grow following previous sterility, or should their number increase, surgical drainage must be resorted to.

Mortality, in the acute streptococcal empyemata accompanying influenza in the 1918 epidemic, was less in those cases treated as long as possible by aspiration. The temperature chart and the clinical condition are, of course, essential guides in judging what course is to be taken.

Where an empyema consists of frank pus surgical treatment is necessary.

Care must be taken, in all cases, to obtain an accurate conception of the bacteriology. A film should be made and

stained by Gram's method, and a second with Löffler's methylene blue; these should be examined personally immediately after exploration. The cells, and often the organisms also, either the lanceolate *Diplococcus pneumoniae*, in pairs or in chains consisting of a few pairs, or else the definite bead-like chains of spherical streptococci, may be easily made out.

If the material is sent to a laboratory, it should be placed in a rubber-capped test-tube; no oxalate is necessary.

Septic Empyema

The empyemata accompanying septicaemias, septic pulmonary conditions, typhoid fever, scarlet fever, &c., contain polymorphonuclear leucocytes, do not clot, and often contain the infecting organism, which is found in films and culture. Empyema in typhoid fever transforms the usual leucopenia into a slight leucocytosis.

Actinomycotic Empyema

The effusion is frequently offensive, and the pus is often semi-gelatinous and viscid in parts. On swilling the fluid round the test-tube little grey or yellowish solid masses, the size of a small pin's head, are left adherent to the glass. These will be found to be composed of mycelial clubs when flattened upon a slide, stained by Gram's method, and examined.

The organism, if sent in a sterile manner to a pathologist, can be grown and a vaccine made. This is not of any definitely proved value, but may in some cases of superficial disease be tried; where organs deep in the body are involved it is probably useless. The pus is often secondarily infected.

EFFUSIONS IN HYDATID DISEASE

The effusion may be clear if there is no secondary infection. Hooklets may be found in the fluid or in the sputum. A definite eosinophilia in the blood is present in many cases. Casoni's reaction (3) is generally positive.

EFFUSIONS IN SYPHILIS

Effusions caused by syphilis are usually serous and sterile. Clotting may be present. The cells present are chiefly epithelial cells and lymphocytes in about equal proportions. The Wassermann reaction is positive in the fluid as well as in the blood. The effusions associated with **aneurysm of the aorta** have various causes, such as pressure on the azygos veins, heart failure, or an associated tuberculosis. They may be blood-stained.

E. BIBLIOGRAPHY

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(2) Bourne & Scott. *Brit. Med. J.*, 1922, i. 387.
(3) See references 5, 6, and 7, Section D.

F. DISEASES OF THE UROGENITAL SYSTEM

XXI. THE ESTIMATION OF RENAL EFFICIENCY.

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CHAPTER XXI

THE ESTIMATION OF RENAL EFFICIENCY

General Considerations

Laboratory evidence of disease of the kidneys is divisible under two heads, according to whether it denotes damage to renal structure or abnormalities of renal function.

Damage to Renal Structure

The only direct evidence of disease of the kidney is the discovery of casts of renal epithelium in the urine. Experience has proved, in addition, that when albumin is found in quantity, i.e. above 0·5 per cent., in the urine renal disease generally coexists.

Haematuria, as an isolated finding, convicts no definite part of the urinary tract; where, however, it accompanies casts or considerable albuminuria it is generally assumed to be of renal origin. The presence of blood-casts proves the bleeding to be renal. The importance of blood is that it is a sign of an open surface, and therefore of active disease. That it arises from the kidney is more probable when it is in intimate admixture with the urine, or when the urine remains of the same tint during the whole action of urination. Where the first urine passed is the more bloody, a lesion of the urethra or prostate is more likely; when the last urine contains most blood, a vesical lesion is more probable. Renal haematuria in nephritis is probably of glomerular origin.

Abnormalities of Renal Function

Pathological evidence of disordered renal function is to be found only when such function is considerably diminished in degree. The findings are divided into two groups depending upon the side of the renal filter on which they are found. Evidence of retention is to be discovered in the blood, and of diminished excretion and impaired power of concentration in the urine. The value of such evidence is

enhanced by the intravenous or oral administration of substances subject to these variations, and by observing at half-hourly or hourly intervals the degree and rate at which their elimination occurs. By comparing the results with known normal figures evidence of value is to be obtained. Natural retention is of graver significance than is artificial retention. A considerable proportion of excreting renal tissue must be destroyed before any functional deficiency is discoverable.

The tests of greatest clinical value in estimating renal function (where disease of both kidneys is suspected) are: the estimation of the fasting blood urea, the determination of the urea concentration factor or of Ambard's coefficient, the urea tolerance test, the urea concentration test, the loss of the normal specific gravity variations, and the water test. The urea concentration test and the indigo-carmine or phenolsulphonephthalein tests, combined with ureteric catheterization, are used where the condition of one kidney is to be determined. In the light of present knowledge it is not possible to be dogmatic in allotting these tests to the different histological constituents of the kidney, but there is some clinical evidence to suggest that the blood urea and urea concentration tests are particularly affected by glomerular, and the water test by tubular damage. Volhard and Fahr's (4) classification of renal disease appears to be the one now most generally accepted. They recognize two essential types, nephritis and nephrosis. Their differentiation rests upon the pathological assumption that the glomerular and interstitial part of the kidney will react differently from the parenchymatous or tubular part to pathological insults. The former will show hyperaemia, swelling, diapedesis of leucocytes, haemorrhage, and all the other signs associated with inflammation, whereas the latter will merely manifest degenerative changes in its cells, such as cloudy swelling, granular and fatty degeneration, and, finally, necrosis. The cause of most cases of nephrosis is obscure; the known causes are identical with those of amyloid renal disease—which manifests an advanced stage of the condition—tuberculosis, syphilis, and continued sup-

puration; those of nephritis appear to be frequently of bacterial origin. On the other hand, a continued nephritis often leads to an associated nephrosis.

It must be remembered, however, that in most cases of acute nephritis all parts of the organ are to some extent affected. Pressure changes resulting from hyperaemia in an encapsulated organ are likely to occur during the acute stage of any type of inflammation. In chronic conditions there is also, as a rule, a lesion affecting both types of structure in varying proportions. Thus in both acute and chronic states a pure nephritis or a pure nephrosis, in terms of the above definition, is rare.

Another factor to be considered with regard to the value of renal function tests is the reserve power of the kidney. Nephrectomy is only rarely followed by signs of inadequacy of the remaining organ, and the tests above described will be insufficient in many cases to prove renal damage, even when this involves two-thirds of the total renal substance. Nevertheless, evidence of urea retention is generally a proof of glomerular inadequacy, and water retention is usually present in tubular disease.

EVIDENCE OF RETENTION IN THE BLOOD

The Blood Urea

The figure given for the normal urea content of the blood three hours after a meal is 20–40 mg. per 100 c.cm. This varies slightly in different individuals; in later childhood and youth the figure being nearer 20, and in middle age nearer 40. In children under twelve, the figure tends to be higher than in adults by about 10 mg. per 100 c.cm. (1). As a rule, 50 mg. as an isolated finding is not outside normal limits. The following factors will cause an increase in the blood-urea figure:

Food.
Renal Disease.
Excessive Loss of Fluid.
Obstruction to Urinary Outflow.
Fever.
Heart Failure.

The cerebro-spinal fluid gives figures practically identical with those of the blood.

Food

The ingestion of an ordinary meal has a definite effect in increasing temporarily the blood-urea content. Blood should therefore be withdrawn at least three hours after food.

The ingestion of urea is followed temporarily by a rise in the blood urea. This rise is of greater duration and degree in glomerular disease, even when the fasting blood urea is normal; its estimation thus provides a more sensitive test.

Renal Disease

When renal disease affects directly or indirectly the glomerular function to a sufficient extent, the blood-urea content is raised. This may occur transitorily in acute nephritis, and may be followed by complete recovery. In chronic nephritis it may be seen during exacerbations or as a terminal manifestation. Uraemia is probably always accompanied sooner or later by a definite increase in the blood-urea figure. The so-called uraemia occurring in eclampsia may often be ascribed to causes other than renal ones, and many of the presumed uraemic symptoms in cases of hypertension are often due to the accompanying hyperpiesis or to small haemorrhages. In each of these examples abnormal urinary findings are present, and may suggest the meaningless label 'auraemic uraemia'.

Excessive Loss of Fluid

Factors that produce a rapid dehydration are apt to produce an increase in the blood-urea figures. Among these are continued vomiting and excessive diarrhoea. Carcinoma of the stomach in a young adult, producing vomiting over a considerable period, wasting, diminished urinary output, and albuminuria, was, in one case, accompanied by a blood-urea figure of over 100 mg. per 100 c.cm., and this led, temporarily, to the incorrect diagnosis of uraemia. Vomiting can cause a rise to as high a figure as 300 mg. Summer diarrhoea of infants may often produce raised

figures. It must be also remembered that both vomiting and diarrhoea can be symptoms of uraemia.

Obstruction to Urinary Outflow

Mechanical causes of obstruction to the outflow of urine from normal kidneys, such as intrapelvic tumours, bilateral renal calculi, enlarged prostate, or urethral disease, are accompanied by an increase in the blood-urea figure if the obstruction is sufficiently severe and prolonged. But the kidneys here are probably also abnormal in most cases.

Fever

A severe febrile disease may, as a sequel to transient renal damage, produce a slight increase in the blood urea.

Heart Failure

This is sometimes accompanied by temporarily slightly increased figures (see p. 296).

The Blood Urea and Prognosis

The blood-urea estimation gives help in prognosis as well as in diagnosis. The absence of any increase during the course of a nephritis which, from other signs, is largely glomerular, is a factor suggesting a good prognosis.

When a rise occurs any increase or decrease in the figure is apt to run parallel with the pathological condition. A blood-urea figure of over 200 suggests a further outlook, as regards life, of months only, and of over 300, of weeks. It occasionally happens that, although the blood urea is somewhat raised, there is some doubt as to whether the symptoms present, frequently cerebral, be due to uraemia, cerebral vascular disease, or to some other non-uraemic cause. In such cases Andrewes's diazo test may be of great value. It is only positive in cases of uraemia (see p. 277).

THE UREA TOLERANCE TEST

A test has been devised by Archer and Robb (2) somewhat on the lines of the glucose tolerance test used in the diagnosis of diabetes. Its rationale is as follows: the kidneys may be damaged, but not to the point of retaining urea in

the blood-stream at above 50 mg. per 100 c.cm. except at times when the amount of circulating urea is abnormally great. If such patients are given orally 15 grammes of urea, this is retained in the blood in greater amount and for a longer period than is the case in normal individuals. Normally the ingestion of this dose of urea causes an increase from the resting level of about 30 mg. to something below 50 mg. per 100 c.cm. of blood. The rise has usually finished in 30 minutes, but occasionally it is not highest until 60 minutes after taking the urea. The urea percentage has returned to the original level as a rule within two hours. Samples of blood are taken 30, 60, 120, and 240 minutes after the injection of the urea. By the use of Archer's micro method (3), these can be taken from an ordinary needle prick, only 0·2 c.cm. being needed.

It is important that the right dose of urea be given, for an increase above this causes a distinct lengthening of the period needed for the return to normal figures. The dose given to children should therefore be correspondingly less. Archer and Robb state, with reference to their normal standards, 'The resting level is normal, the rise is 5–15 mg. in 30–60 minutes. The recovery is complete in 120 minutes.' The point they particularly stress is the recovery, i. e. the return to the normal figure within two hours. Abnormally delayed recovery was found by them, not only in all cases with nephritis and a raised blood urea, but in patients whose blood-urea figure and urea concentration test were both normal, but in whom there was evidence of recent renal disease. The recovery time is often as long as four hours in such cases.

It would appear that this test is applicable to all varieties of nephritis in whose more severe stages a raised blood urea is to be expected. It is distinctly more delicate, revealing evidence when the resting blood urea is normal. It is strongly positive in cases which have already a raised blood urea, but in them it provides no additional information.

Like other renal function tests a comparison of results obtained at intervals of time will often give more information than will the figures of one isolated test.

AMBARD'S COEFFICIENT

This test attempts to measure the relation that renal excretory activity bears to the blood urea on the one hand, and to the urine urea upon the other. Ambard, as a result of experimental work, formulated three laws with regard to renal efficiency; they are briefly:

1. The rate of output of urea varies directly with the square of the concentration of urea in the blood, if the concentration of urea in the urine remains constant.

2. The rate of excretion of urea varies inversely with the square root of the concentration of urea in the urine, if the blood urea remains constant.

3. If the concentration of urea in the blood and urine varies simultaneously, the rate of output will vary directly as the square of the concentration of urea in the blood, and inversely as the square root of that in the urine.

The following formula is used:

$$K = \frac{Ur}{\sqrt{D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}}}$$

K = coefficient of urea excretion.
Ur = grammes of urea per litre in blood.
D = output of urea (grammes per litre) for 24 hours.
P = weight of patient in kilos.
C = grammes of urea per litre in urine.
70 = standard weight.
25 = standard concentration of urea in urine.

K = 0·06 to 0·09 normally.
Inadequate excretion raises the figure.

This formula enables the renal function to be estimated from data on both sides of the renal filter and will, like the urea tolerance test, show deficient excretion even when the actual blood urea is not increased. The test is carried out three hours after a meal. The bladder is emptied and the patient waits an hour; the bladder is again emptied and blood is withdrawn for a urea estimation; the bladder

is once more emptied at the end of a second hour. The volume of the urine and the urea content are measured for both hour periods. The patient is weighed. All data are then ready for the working out of the formula, for the amount of urea passed in two hours gives a basis for estimating the twenty-four hour quantity. Coefficients of between 0·06 and 0·09 are regarded as normal; low figures are often found in febrile diseases, hyperthyroidism, early arteriosclerosis, and nephrosis. In cardiac failure and passive congestion, the figure is usually raised during the period of decompensation, averaging about 0·12, even when the blood-urea figures are normal.

In renal disease, the figures are increased according, apparently, to the degree of glomerular damage; also, in other conditions in which the blood-urea figure is raised. The increase often occurs a considerable time before the blood-urea figure changes. Variations in the figure approximate closely to changes in the clinical state. The range of variation is between the normal figure and about 1·4. Though no deductions of value can be drawn from any single laboratory test as regards prognosis, it may be stated that a figure below 0·15 does not suggest an immediately serious lesion, and that a figure above 0·2 does suggest a rapidly fatal outcome. It must be remembered that one fixed point will not give the direction of a straight line, and that a series of comparable results is generally of greater value. There is some doubt as to whether the test will give any more information than can be obtained from the blood urea and the urea tolerance test. MacLean considers that what he describes as the Urea Concentration Factor is of greater practical use.

THE UREA CONCENTRATION FACTOR

The relation between the percentage figure of urea in the urine to that in the blood, both expressed as milligrams per 100 c.cm., is known as the urea concentration factor. Normally this figure should be in the neighbourhood of 70.

The number is diminished in some cases of nephritis, and when the figure falls below 12 the condition is grave. In-

formation of most value can be obtained by comparing results from time to time.

The technique of the test is as follows: The patient has taken no food for three hours. The bladder is emptied, blood is removed from a vein, and the bladder is again emptied at the end of an hour. The urea content of these last two specimens is estimated.

EVIDENCE OF IMPAIRED POWER OF CONCENTRATION

The Urea Concentration Test

This test, devised by MacLean, is a measure of the extent to which the kidneys are able to concentrate urea. It is performed in the early morning upon an empty stomach, the patient being confined to bed. His bladder is emptied and immediately he is given to drink 15 grammes of urea in 100 c.cm. of water. The urine is then collected hourly for three hours, and, together with that passed just before the test, is sent to the pathologist carefully labelled and in separate bottles. The normal kidney is able to concentrate to a solution of over 2 per cent. of urea, and generally does so in all the specimens examined. There is one exception to this in the occasional diuresis caused soon after the urea administration. In such cases the first hour's specimen is sometimes of a lower percentage than 2, but the volume of that specimen is proportionately great. It is thus important to measure the amounts passed as well as to send samples of each for the estimation of their urea content. Urine urea figures of over 2 per cent. exclude the presence of uraemia.

The test is of value in estimating renal damage, and, more particularly, in assessing changes in the patient's condition. It shows sometimes the presence of renal inefficiency after the blood urea has returned to normal. It is difficult to weigh the evidence of the test as deciding between glomerular or tubular guilt. In children 10 grammes are given instead of 15. Syrup of lemon makes a good flavouring for the mixture.

The Concentration Test

This test, originally devised by Volhard (4) and modified by Fishberg (5), appears to give a reasonable measure of the

concentrating power of the urine, especially in cases of chronic nephritis and in renal sclerosis. It has the merit of great simplicity. In the words of the latter: 'About 6 o'clock of the evening before the test, the patient has his usual supper, which should not contain more than about 200 c.cm. of fluids. After this he neither eats nor drinks anything until the tests are over. Before retiring he empties his bladder; this urine is discarded. On wakening in the morning he passes urine, which is kept in a separate bottle. He remains in bed and urinates one hour later, and again an hour after this, each urine being kept in a bottle. The specific gravity of each of the three specimens is measured, and the highest taken as the patient's maximum. If kidney function is unimpaired the specific gravity will exceed 1,025, often going as high as 1,032. In the severest impairment of renal function the specific gravity is only 1,010, and in intermediary cases figures between these extremes are obtained. In patients with true uraemia the maximum is under 1,020, and usually much closer to 1,010. In every case with a low specific gravity it is important to observe whether oedema is being evacuated, for this may simulate inability to concentrate.'

EVIDENCE OF IMPAIRED WATER EXCRETION

The Water Test

The test is a simple clinical measure of the eliminating power of the kidney for water. It is found to be deficient in hydraemic types of nephritis or in nephrosis. The patient, who is confined to bed, as in the urea concentration test, empties the bladder in the early morning, the stomach being empty. A drink of $1\frac{1}{2}$ pints of water is immediately given, and the bladder is emptied at each subsequent $\frac{1}{2}$-hour period for $2\frac{1}{2}$–3 hours. The volume of each specimen is measured. In the absence of renal disease there is a diuresis that is maximal in the first, second, or third specimens. When renal damage as regards water elimination is severe, no diuresis at all is evident, the volumes remaining practically equal throughout. In the intermediate stage the diuresis is less marked in degree and comes at a later period, both of

these factors depending upon the severity of the lesion. With this test, as with the previous one, several comparative results in a single case are of greater value than is a single result.

OTHER TESTS

The Phenolsulphonephthalein Test

Intramuscular injection of 1 c.cm. of a solution of phenolsulphonephthalein is in normal people followed by excretion of 50 per cent. at least within two hours. Each cubic centimetre of the solution contains 6 mg. of the dye. The bladder is emptied just before the injection and the patient is given a drink of water. The urine is collected 1 hour and 10 minutes and again 2 hours and 10 minutes after the injection, and the two specimens are sent to the pathologist, who estimates the amount present in each by a colorimetric method.

The test appears to be relatively unchanged in nephrosis and is changed in nephritis according to the extent of the damage. Comparative readings are probably of greater value than are absolute figures.

Ability to excrete phenolsulphonephthalein must not be taken necessarily as proof of ability to excrete other substances. The evidence is not more than circumstantial. The test is easily done but not very delicate. In normal people the figure for the first hour's specimen is in the neighbourhood of 50 per cent., and for the second of 25 per cent., giving a total for the two specimens of 75–80 per cent. The less the total figure the greater is the damage. Evidence as to rate of excretion is to be found in the proportions excreted in each hour. The slower the excretion the less proportionately is excreted in the first hour.

The Diazo Test

Andrewes (6), in 1924, whilst engaged in investigations upon the van den Bergh reaction, noticed a diazo colour reaction which was present only in uraemia. Hewitt, Rabinowitch, Blotner, Fitz, and others have confirmed the results that he obtained. Harrison (7) has summarized the published cases, which amount in all to some hundreds.

The details of the test are described elsewhere. Briefly, the facts are as follows: owing to the inability of the damaged kidney to excrete some unknown substance, possibly a cyclic amine, the blood-serum retains this and gives a positive test.

The reaction occurs only in uraemia or in severe renal inadequacy, but not in all cases. It may occur when the blood urea has as yet not risen to 100 mg. per cent. It may allow a correct diagnosis of uraemia to be made when cerebral symptoms are present, which suggest equally that diagnosis and arteriosclerosis or haemorrhage.

Blotner and Fitz state that a high blood urea is not so significant, as regards a serious prognosis, if unaccompanied by a positive diazo test.

The reaction is apparently not peculiar to any particular type of nephritis. Its appearance in an already uraemic patient adds to the seriousness of the prognosis.

The substance has not been found in the cerebro-spinal fluid.

In addition to their usefulness as determining diffuse lesions of the kidney, renal function tests have a further field of utility. Certain diseases of the kidney are unilateral and are to be treated by surgical means. If the urine be collected simultaneously from both kidneys, by means of ureteric catheterization, the diseased side may be convicted, the extent of the lesion may be deduced, and the health of the presumably sound side may be proved.

This measure should be employed in all cases where a nephrectomy is in contemplation.

CHAPTER XXII

DISEASES OF THE KIDNEY

ACUTE NEPHRITIS

Acute nephritis of whatever kind will produce abnormal pathological findings in two ways. Either the diseased tissues, as a result of local inflammation and coexistent swelling of the organ as a whole within its fibrous capsule, will fail to eliminate substances, which will be retained in the blood; or else the products of the local renal destruction will appear in the urine. The degree to which the first of these occurs will depend upon the severity of the inflammation and its extent. In most cases of acute nephritis which are at all diffuse some suppression occurs. In acute focal nephritis the signs are entirely urinary.

ACUTE DIFFUSE NEPHRITIS

The following are the common pathological findings in severe acute diffuse nephritis. The tests printed in italics are generally of most use.

I. Signs of Deficient Excretion.

Oliguria.
Delayed Recovery in the *Urea Tolerance Test.*
Increased Fasting *Blood Urea.*
Increased figure for Ambard's Coefficient.
Decreased Urea Concentration Factor.
Deficient *Urea Concentration Test.*
Deficient *Water Test.*
Diminished Chloride Excretion.
Impaired Phenolsulphonephthalein Excretion.
Positive Diazo Test (in uraemia).

II. Signs of Renal Damage.

Haematuria.
The Presence of White Blood-cells in the Urine.
The Presence of Renal Epithelial Cells in the Urine.

The Presence of Casts (red and white blood-cell casts, epithelial, granular, and hyaline casts) in the Urine.

Albuminuria.

III. Other Findings.

Anaemia.

Leucocytosis.

Bacteriuria.

Signs of Deficient Excretion

Oliguria

The severer the case the greater will be the suppression of urine and the longer will this persist. Conversely, the cases with little or no suppression, or with diminution for only a day or two, are correspondingly mild. Frequently the oliguria corresponds with a raised blood-pressure and a change in pulse-rate to a figure either below or above the normal. After a certain length of time these abnormalities may manifest an abrupt change. Within twenty-four hours the blood-pressure falls, the pulse-rate returns to normal, and the urinary output is increased. These 'crises', particularly in children with severe acute nephritis, are not uncommon. Whether they are due to physical or functional changes is not clear.

Blood Urea

The blood urea in mild cases of acute diffuse nephritis is unchanged; in the severer cases it is slightly increased for a length of time varying with the duration of the acute stage of the disease (the increase is frequently to not more than 70 mg. per 100 c.cm.). In the most severe cases the increase is considerable, from 100 to 300 mg. The higher the figure the more imminent are the severer manifestations of acute uraemia. High figures in acute nephritis are of less serious import, especially in children, than is the case in the chronic types of the disease.

If the crisis can be surmounted by purgation, diaphoresis, or bleeding, there is a reasonable chance of a good, and in children of a complete, recovery. Ambard's coefficient and

the urea tolerance test give a similar but more sensitive measure.

Should the blood urea be raised a better prognosis is suggested if, at the same time, the diazo test is negative.

Urea Concentration Test and Water Test

The urea concentration test is of greater clinical value in subacute or in chronic nephritis, for it is then that as many data as possible are needed to estimate the course that the disease is taking.

The two points of doubt, in acute nephritis, upon which knowledge is required are: Is the patient going to die? and, What is the degree and rate of progress of the actual renal damage?

The blood urea and the powers of water elimination are the factors of greatest value in trying to estimate the answer to the first, and the microscopic findings to that of the second problem. When the active damage has been done and the acute inflammatory process has ceased, the problem is changed. The chlorides are diminished in the urine in the more severe types of acute nephritis. The diminution tends to be proportional to the severity of the attack. Comparisons should be made between separate twenty-four hourly specimens.

The Phenolsulphonephthalein Test

This test has a certain value in estimating the severity of an acute nephritis. Failure to excrete any of the drug after two hours is evidence of a severe lesion. The nearer to 50 per cent. is the total excretion figure within a two-hour period, the nearer to normal is the excreting power for the drug. It is a test that is easy and rapid to perform, but will not show fine gradations.

The blood calcium is often diminished in acute nephritis.

Signs of Renal Damage

Haematuria

Haematuria in nephritis is the surest sign of an active lesion. It is, in amount, generally proportionate to the

severity of the local inflammation. Where, however, as in some scarlatinal cases, the lesion is largely interstitial in position, the amount of blood in the urine is often considerably less than might be expected from a knowledge of the pathological condition. Again, in severe suppression some of the blood remains lodged in the damaged organ. The blood, in acute nephritis of whatever type, should be watched from the stage of haematuria, through that of microscopic presence of red blood-cells in the centrifugalized deposit, to that of final complete disappearance, before the lesion can be pronounced inactive. Rest in bed is generally regarded as essential while red cells persist in the urine.

Leucocytes in the Urine

Leucocytes are frequently found in small numbers in the urine of cases of acute nephritis. Their presence in quantity should suggest the possibility of a pyelitis in addition (see p. 301).

Renal epithelial cells are often found in acute nephritis. Their presence, like that of casts, is proof of a renal lesion, but they have no bearing upon prognosis. The renal epithelium is capable of considerable regeneration.

Casts

Red blood-cell casts are found most commonly during the acute stage of a nephritis involving the glomeruli. They are evidence that bleeding is into the renal tubules or Bowman's capsule. It is rare to find them in other conditions causing renal haematuria, such as tuberculosis, neoplasm, and renal infarction.

White blood-cell casts are found in numbers in certain types of acute nephritis. They are frequent in ascending pyelonephritis. When present they indicate an active renal inflammatory process.

Casts formed of renal epithelium are direct evidence of a renal lesion. They are found most commonly in renal disease where a degenerative tubular lesion coexists with an inflammatory one involving the other renal structures

or, in the terminology of Volhard and Fahr, where a nephrosis occurs with a nephritis. They are also found in large numbers in nephrosis. Their presence obviously indicates a shedding of valuable tissue, and therefore a patient showing them should be confined to bed until they are no longer to be found. This rule, however, is less strict than is that referring to the presence of red blood-cells.

Granular and hyaline casts are found so frequently in normal individuals after exertion, and in other pathological conditions involving congestion of the kidneys, that their presence in small numbers in acute nephritis has no bearing upon prognosis, diagnosis, or treatment. In quantity their numbers are to some extent proportional to the severity of the lesion.

Other Findings.

Some degree of anaemia is present in the more severe cases of acute nephritis. Haemoglobin estimations may help to throw some light upon changes in the patient's general condition. Leucocytosis of a slight degree is frequently present. Bacteria are in most cases not found, but their presence or absence in a catheter specimen is worth investigating.

Conclusions

Cases of acute nephritis will show urinary changes resulting from renal damage, with or without evidence of impaired elimination. Where the latter exists attention is mainly directed to gauging its extent and its increase or diminution. The blood-urea tests and the urinary output will give the clearest information upon this from the point of view of clinical pathology.

When elimination is restored, or in cases where it has never been curtailed, attention is directed to the urinary findings. Each of these, blood content, the presence of casts, epithelial cells, and albumin, is watched quantitatively as it in turn disappears. When, short of final disappearance, any one of them reaches a base line, which it maintains in spite of rest in bed and other measures, the

effect upon it of changes in diet and exercise should be carefully watched.

The persistence of red blood-cells as a rule indicates that the renal disease is still active, of epithelial casts that tubular exfoliation is still occurring. Albuminuria alone, of constant degree, probably indicates some local scarring or abnormal permeability, but may have no evil significance.

ACUTE FOCAL NEPHRITIS ('Haemorrhagic Nephritis')

This disease is generally coexistent with some septic process such as tonsillitis, an otitis media, a streptococcal or pneumococcal pyogenic lesion or an impetigo, in contradistinction to acute diffuse nephritis, which, when it is secondary, as after scarlet fever or diphtheria, generally follows at an interval of three weeks or so.

The lesion appears to be glomerular and local; insufficient renal intracapsular swelling occurs to produce any deficiency in elimination, nor is enough renal tissue involved to effect this.

The Pathological Findings are thus entirely urinary; they are:

I. Haematuria.
II. The Presence of Casts.
III. Albuminuria.

Haematuria is often considerable and is the main clinical feature of the disease. The renal bleeding is, in comparison with other forms of nephritis, out of proportion to the other urinary abnormalities. It persists for a variable period, and its disappearance in many cases is followed by a rapid vanishing of the casts and albumin. White blood-cells are sometimes present in fair numbers.

Casts are in the earlier stages largely red-cell casts. After the first few days no further casts may be found. If, however, the lesion is more severe, a few epithelial casts may be seen. Granular and hyaline casts often occur, but vanish rapidly.

Albuminuria is, as a rule, not so considerable as is the case in diffuse acute nephritis or in nephrosis. With the

subsidence of the acute stage of the disease, the albumin diminishes rapidly in amount, and, within a few weeks or even days, has often completely disappeared.

Mild types of the disease are common in children; adults generally display a more severe and protracted form.

ACUTE NEPHROSIS

The chief example of acute nephrosis is seen in poisoning by mercuric chloride. In this condition there is a pure degeneration of the tubular epithelium, and, theoretically, the manifestations of an uncomplicated nephrosis might be expected. These are oedema, albuminuria, and cylindruria, without other evidence of excretory deficiency. There are two complicating factors that tend to obscure the picture: the abruptness and severity of the renal insult, and the accompanying diarrhoea. Owing to the former there is as a rule some swelling of the kidney, and probably some choking of a number of the tubules. Thus not infrequently this lesion is accompanied by some retention of nitrogenous products, as shown by a raised blood urea, and by a lesser amount of oedema than might otherwise be expected.

Pathological Findings

I. Raised Blood Urea.
II. Diminished Renal Function.
III. Decreased Phenolsulphonephthalein Excretion.
IV. Albuminuria, Casts.
V. Anaemia.

The diminished renal function is at its maximum at the onset, and an improvement in the patient's condition runs parallel with a fall in the blood urea. The blood-urea figure is frequently normal; when raised the increase is as a rule not great. Anuria is present in the severe cases, and the prognosis is more serious in its presence.

Epithelial casts are generally present in great numbers, many of them being degenerate. Granular and hyaline casts are also found. Their disappearance from the urine, if the output is not diminished, is a sign that the epithelial desquamation has ceased.

As the patient recovers, the **albuminuria** will decrease. So long as diminution in its quantity persists, confinement to bed should be insisted upon.

A severe **anaemia** is not infrequent. It is due partly to the severe intestinal haemorrhages that often occur, and possibly also in part to a direct toxic action upon the red cells or bone-marrow.

CHRONIC NEPHROSIS

The signs of nephrosis are added to the clinical picture in many cases of acute and chronic nephritis.

Pure chronic nephrosis is a somewhat rare condition. Its commonest discoverable causes seem to be chronic sepsis, tuberculosis, and syphilis, as is the case with amyloid disease. The causes of nephritis will frequently give rise to an associated nephrosis. The kidney of pregnancy has many features of a nephrosis, but is not infrequently associated with a preceding chronic nephritis. Where generalized oedema, albuminuria, and the presence in the urine of casts—epithelial, fatty, granular, and hyaline—are found in a patient in whom there is no evidence of nitrogenous retention or of cardiovascular disease, nephrosis must be deemed to exist. The blood of patients with nephrosis characteristically contains reduced plasma proteins and an excess of cholesterol, and its composition suggested to Epstein (8) the treatment by the diet rich in proteins associated with his name.

Pathological Findings

I. Renal Function Tests.

II. Urinary Contents.

The **renal function tests**, in the absence of an associated nephritis, show: no increase in the blood urea, no inadequacy in urea concentration, and no retention of phenolsulphonephthalein. The water test frequently shows inadequate excretion of water. Should nitrogenous retention occur, the prognosis becomes considerably more grave.

The **urine** shows the presence of epithelial, fatty, granular and hyaline casts, and considerable quantities of albumin.

Red blood-cells are not present. Amyloid material is an extremely rare finding in the urinary cellular content even in the presence of amyloid disease of the kidney.

In all cases foci of sepsis, syphilis, and tuberculosis must be ruled out.

Anaemia is not a result of nephrosis, though it may be caused by the associated condition, such as syphilis.

CHRONIC NEPHRITIS

The title 'Chronic Nephritis', as generally used, includes two main groups: that which follows a definite inflammatory condition, and that which appears to be secondary to progressive arteriosclerotic lesions affecting the arterioles feeding the glomeruli. The tendency latterly is for the first group to retain the label nephritis and for the latter to be called renal sclerosis. This classification is adhered to in the following account. Seeing that raised tension and arteriosclerosis appear so frequently in cases of acute and chronic nephritis respectively, and seeing that areas of inflammatory reaction are found so constantly microscopically in the small red or granular kidney, there is a temptation, particularly on the part of histologists, to try to amalgamate the groups under the title of mixed nephritis. It should, however, be remembered that the kidney of renal sclerosis is a damaged, vitally impaired organ, and yet, as part of its normal duties, it excretes living organisms to some extent from normal blood. Seeing that its powers of local resistance are presumably damaged together with those of local excretion, areas of inflammatory change are to be expected.

The difference in the clinical course in either case suggests that it is wise to keep the two groups, inflammatory and vascular, separate. By chronic nephritis in this chapter is meant a chronic renal condition, inflammatory in origin, with or without renal oedema according to the presence or absence of nephrosis, with or without signs of renal insufficiency according to the stage of the disease and the adequacy of cardiovascular compensation, and which is characterized post mortem by the condition known variously

as the contracting or contracted white kidney or secondary chronic interstitial nephritis, and microscopically by lesions that chiefly show glomerular and interstitial disease.

The course of pathological events appears to be as follows. As a result of some inflammatory condition elsewhere in the body, such as tonsillitis, otitis, sinusitis, infected wounds, erysipelas, or as a sequel to scarlet fever or purpura, the infecting agents or their toxins produce acute inflammatory lesions of the glomeruli either directly or indirectly. This acute stage is followed by a chronic one of fibrosis which is not infrequently progressive.

There are three alternative clinical courses run by the process:

(A) The symptoms and signs of the acute stage never subside, and the disease proceeds without intermission to chronicity, and eventually to death.

(B) The acute stage occurs and is followed by an intermission, as regards symptoms, for a variable period.

(C) The acute stage passes unnoticed, but, after a period, symptoms and signs of chronic nephritis become manifest, generally abruptly and in the shape of uraemia.

Pathological Findings

(A) In the case where the chronic stage follows the acute without an interval, the signs of nephrosis are generally added to those of nephritis. In this type, therefore, the pathological findings will be as follows:

Signs of Renal Inadequacy. After subsidence of the acute process the blood urea at first will not be raised. The reason for this is that for recovery from the acute stage to have been possible, the damage to the kidneys is necessarily below a certain amount. At the end of the acute inflammatory process with the disappearance of swelling and hyperaemia, many of the glomeruli, whose disfunction is purely mechanical, resume their work. Moreover, a certain number of the actively inflamed glomeruli probably recover, at least temporarily. Thus the renal function is carried on

by an adequate staff for the first stage of the chronic disease. There is, however, a second process in operation. Either as a direct sequel to the presence of the diseased tissue and fibrosis left behind after the acute process, or more probably because the cause of the original acute nephritis remains active, there will occur a slowly progressive lesion resulting in hyperplasia and, eventually, in fibrosis of the unaffected glomeruli.

For a time this gradual decimation remains unnoticed by the body, but eventually, for adequate elimination to occur, compensatory processes arise. The first of these to be noticed, at the stage where the kidney begins to be less able to concentrate the urine, is nocturnal increased frequency and a lowering of the specific gravity. The second is manifested by cardiovascular changes. The blood-pressure becomes raised and cardiac hypertrophy results. The powers of elimination, however, still remain adequate.

The final stage supervenes when, as a result of extension of the renal disease, or following upon some degree of heart failure, the excretory powers become inadequate. The blood urea remains at a normal or slightly increased figure during the course of the disease until this last phase, when it will progressively and rapidly rise. The urea concentration test, a positive urea tolerance test, or some fixation of the specific gravity to near 1,012 will sometimes show evidence of dysfunction before the blood urea rises, but conclusions can only be safely drawn by comparing a series of results. An isolated finding will give no help in trying to determine any change of condition. If in addition to the raised blood urea the diazo test is positive the immediate prognosis is worse than if this were not the case.

Urinary Findings. A moderate degree of albuminuria is present in compensated and uncomplicated cases. A heavier cloud follows heart failure during chronic nephritis, or accompanies nephrosis. Red blood-cells are generally present, as the process is one of slowly progressive activity. White blood-cells are to be found. Casts, chiefly granular and hyaline, occur, but not in large numbers in the absence of heart failure or nephrosis.

Most cases of chronic nephritis that follow an acute attack without an interval are associated, from the first, with a greater or lesser degree of nephrosis. The generalized oedema, pronounced albuminuria, and abundance of epithelial and fatty casts, indicate a considerable nephrosis. The specific gravity of the urine may be higher than would be expected at a similar stage of a pure nephritis. There is also very considerable deficiency in the excretion of salt. With the progress of the disease the symptoms and signs of nephrosis often tend to disappear.

(B) In those cases where an interval of freedom from symptoms intervenes between the attack of acute nephritis and the onset of the chronic disease, an examination of the patient during the interval would probably show a renal function that was within normal limits. Possibly there would be demonstrable some limitation as regards the urea concentration and water tests, the presence of some albuminuria, an occasional cast, and perhaps also in the centrifugalized deposit a few red or white blood-corpuscles. The continued absence of the red and white blood-cells, with normal renal function tests, would, in the absence of symptoms and cardiovascular changes, but in the presence of the other urinary findings, indicate that the previous acute attack had produced damage, but that the only signs present were those of a scarred kidney. In all but these arrested cases, however, the progressive glomerular changes would occur as described in the previous section, and similar abnormalities in renal function and in the urine would be discoverable with the progress of the disease. Should the hypertrophied heart fail, to a greater or a lesser extent, the result will be increased albuminuria and a greater number of casts and possibly of red blood-cells in the urine.

(C) These cases, preceded by no history of acute renal disease, are probably identical with the small white kidney described by Rose Bradford. The original nephritis passes unnoticed and is followed by a progressive, slow destruction of glomerular tissue. As a rule, oedema, with the other signs of nephrosis, is absent. While there remains an adequate number of glomeruli, no further abnormalities

occur, but, when the disease passes this point, symptoms arise. They are most commonly due to uraemia or to retinal changes, and are accompanied by raised blood-pressure and cardiac hypertrophy. Before the failure of renal efficiency, the only pathological signs will be urinary and haemic.

Urinary Signs. The specific gravity of the twenty-four hour specimen is frequently low; it may become fixed at a figure of about 1,012 in all the specimens examined. Albumin is present in variable amounts from a trace to a fairly heavy cloud. If there is any cardiac failure it is immediately increased. Hyaline, granular, and possibly fatty casts are present. Red and white blood-cells may be found. They may be increased in cardiac decompensation. After the excretory powers have begun to fail, evidence of this will be found in a raised blood urea and poor results in both the urea concentration and water test. The order in which these findings occur varies in different cases.

Blood. There is almost always to be found a secondary anaemia of the chlorotic type. The severity of this gives some indication as to the degree of toxaemia, and, therefore, is of considerable assistance in prognosis. A persistent haemoglobin figure of less than 60 per cent. in these cases appears to be of serious significance.

THE KIDNEY OF PREGNANCY

The renal disorders complicating pregnancy belong to one of three types: Albuminuria, the 'Nephritic Toxaemia' of de Wesselow, and the Pregnancy Kidney.

Albuminuria frequently accompanies pregnancy. It is accompanied by no evidence of excretory failure or of renal damage. It may be due to causes similar to those producing functional albuminuria and is comparable with this (see p. 312).

The Nephritic Toxaemia is a name given to an exacerbation by pregnancy of an already existent nephritis. The accentuation of the condition is particularly in the direction of retention of urea and of toxic products. A close and care-

ful watch should be kept upon the blood urea upon the one hand, and upon the evidence of renal damage upon the other. A definite rise in the blood-urea figures is a strong indication for the termination of the pregnancy, for, even if mother and child both survive, the existing nephritis is generally very considerably accentuated. The pathological findings are those described under chronic nephritis, and similar deductions can be made from them as regards diagnosis and prognosis. It must be remembered, however, that the toxaemia of pregnancy is an intensifying factor.

The 'PREGNANCY KIDNEY' is probably in most cases a nephrosis, evidence of impaired renal function being absent although albumin and casts are present in considerable quantity in the urine. In such patients the pregnancy can generally be safely allowed to go to term. But they must be kept under close observation, for, as the name sometimes given to them—pre-eclamptic toxaemia—suggests, true eclampsia may manifest itself. Though the onset of eclampsia is occasionally heralded by an increase in the blood urea this is not invariably the case, but a warning sign is sometimes given by the presence of bile pigments and urobilin in the blood and urine (9).

RENAL SCLEROSIS

Arterial disease affects the kidney in two different ways. The changes are either fine, and diffusely spread through both organs, or else tend to be gross and localized. In the first group is placed the small red kidney, red granular kidney, chronic interstitial nephritis of Bright, or gouty kidney; the second group comprises the focal arteriosclerotic kidney. These two types may be designated as diffuse and focal renal sclerosis. The former is a serious disease producing raised tension and all the evils that follow in its train, cerebral, cardiac, and uraemic. The latter is a local destruction of renal tissue, sufficient normal structure remaining for adequate excretion; the only manifestations are urinary, and essentially unimportant.

DIFFUSE RENAL SCLEROSIS (Small Red Kidney, Granular Kidney)

The essential causative lesion is a progressive arteriosclerosis affecting the smallest renal arteries and arterioles. Consequently, the blood-supply is slowly but finally withheld from successive numbers of glomeruli throughout both kidneys. There is, therefore, in these cases, no history of an originating acute nephritis. Owing to the great reserve of renal excretory tissue, the earlier stages of the disease pass without signs or symptoms. Eventually, the glomerular numbers will have become so diminished that excretory changes will occur. The earliest of these is deficient power of concentration, manifested by night polyuria and a fixation below a certain figure, generally 1,015, of the specific gravity of the urine.

The renal changes may be part of generalized arteriosclerosis, but, in any case, the condition is followed or accompanied by a progressive increase in the blood-pressure and a concomitant cardiac hypertrophy. It is this added cardiovascular burden that, in most cases, causes death, heart failure or cerebral haemorrhage resulting; but should heart and vessels withstand the additional strain death comes from glomerular inadequacy and uraemia.

Pathological Changes

Before there is any failure in renal excretion the pathological findings are chiefly urinary; afterwards they are both urinary and haemic.

Stage I. Before renal failure.

Urine

There is generally polyuria. Nocturnal frequency occurs. The specific gravity becomes lowered and is due to inability of the kidney to concentrate. This is well shown by the concentration test (see p. 275). Renal efficiency tests at this stage may show no other abnormality. The urine may or may not contain a trace of albumin. A few granular and hyaline casts may be found. Haematuria, gross or

microscopic, is an affair of not infrequent occurrence. A few leucocytes may be found.

Blood

If there is any change at all in the blood picture at this stage it is in the direction of slight polycythaemia.

Should heart failure supervene, to the urinary picture will be added an increase in the number of casts and cells and in the amount of albumin.

Stage II. After the advent of renal inadequacy the following abnormalities are found:

Renal Function.

The urea tolerance test is positive, and later the blood-urea figures are raised. Changes in these figures should be watched carefully, as they will be a good guide as to the progress of the disease. It is in the interpretation of the cerebral symptoms common in the disease that the diazo reaction is of great use. A positive result in such cases proves the presence of uraemia, a negative one points to a vascular cause. The urea concentration test, the water test, and the phenolsulphonephthalein test also show impaired powers of elimination.

Urine

The specific gravity is lower and the polyuria and nycturia greater than in the former stage. The albumin content is slightly more than before. Casts of all kinds, but chiefly granular and hyaline, are found in small numbers.

Blood

The terminal stages of the condition are sometimes accompanied by a secondary anaemia.

FOCAL RENAL SCLEROSIS

This is a condition in which, as a result of arterial disease, certain areas of renal tissue are deprived of their blood-supply. It differs from diffuse renal sclerosis in that the lesion is restricted to a comparatively small number of

vessels larger in size than is the case in the latter condition. The result is that, although, post mortem, the kidney appears to be rather grossly deformed, there remains a functionally sufficient amount of normal renal tissue. There are, therefore, associated with the lesion no signs of cardiac hypertrophy or of raised blood-pressure. From time to time gross haemorrhages may, in a small number of such cases, occur. If nephrectomy for severe renal haematuria be made the object of search in any sufficiently large series of cases, examples of this disease will be found among them.

Pathological Findings

These will be urinary only. The specific gravity and quantity are normal. The renal function tests are normal. A trace of albumin is often present, the quantity being increased by exercise. A few hyaline and granular casts may be found in the centrifugalized deposit. Blood will be found in quantity in connexion with an attack of macroscopic haematuria. As a rule no erythrocytes are present between such attacks, though, in occasional specimens, their presence in small numbers in the centrifugalized deposit is not necessarily significant.

POLYCYSTIC RENAL DISEASE

The aetiology and cause of this condition is obscure. It would appear that the progressive cystic formation runs coincident with a gradual diminution in the amount of functioning renal tissue. As in chronic nephritis, this diminution is associated at first with cardiovascular changes —cardiac hypertrophy and raised vascular tension— and later on with an impairment of renal function. This is manifested in the same manner as in chronic nephritis. The urinary findings are slightly different, in that casts are generally absent. Haematuria occasionally occurs at any stage of the disease.

Urine.

The amount is increased except in the terminal stage. The specific gravity is generally unaffected at first, but, with the

advent of cardiovascular adjustments, it tends to become lower and to approach a figure of less than 1,015. Albumin may be absent. If present it is only in small amount, except in association with a failing heart.

Casts, granular and hyaline, are generally absent, but may be found in a centrifugalized deposit. Red and white blood-cells may be similarly discoverable, but they are frequently absent. Occasional gross haematuria, if it occurs, will, of course, flood the urine temporarily with blood.

RENAL CONGESTION

Congestion of the kidney results from any causes that produce over-distension or stasis of the renal vein. The commonest cause is chronic passive congestion resulting from heart failure; other rarer causes are: obstruction to the inferior vena cava by chronic mediastinitis, mediastinal tumour, increased intraperitoneal pressure, or malignant tumours of the retroperitoneal tissues or liver. Congestion also occurs in epileptic convulsions, and its findings may suggest wrongly the diagnosis of uraemia. Unilateral congestion may occur in severe displacement of the organ.

The Pathological Findings are chiefly urinary:

Urine

In slight or briefly persisting congestion slight albuminuria alone is found. In more severe cases this is more pronounced, and hyaline and granular casts occur. Where the congestion is severe and persistent, as in gross cardiac failure, the albuminuria and granular and hyaline casts are present in quantity. Epithelial and fatty casts do not appear apart from nephritis. Blood casts are not found. Red and white blood-cells may be seen in small numbers; any gross haematuria should suggest the presence of an infarct. Urates are generally present in quantity in the urine of heart failure.

Blood Urea

The blood urea in uncomplicated cardiac failure is rarely raised above 60 milligrams per 100 c.cm. of blood, and this

figure becomes rapidly less with an improvement in the circulation. Slighter changes are detected by use of the urea tolerance test.

The Other Tests

Urea concentration and phenolsulphonephthalein show similar slight impairment during the period of failure, with a rapid return to normal as the cardiac mechanism becomes more efficient. The water test is similarly but more readily affected.

When a slight degree of loss of eliminatory power, as shown by these tests, is coupled with definite signs of heart failure, the former is probably due to passive congestion, if a rapid return to normal figures coincides with disappearance or definite diminution in the signs of decompensation. The causes, other than cardiac, of renal congestion rarely produce more than albuminuria and the presence of a few granular and hyaline casts. The renal function in such cases is not impaired.

RENAL INFARCTION

The pathological signs of renal infarction are urinary when they occur, and are characterized by the sudden appearance of blood, varying in quantity with the size of the infarct, albuminuria of a slight degree, and the presence in the urine microscopically of red cells and a few leucocytes. Casts are rarely seen. These abnormal appearances in the urine, as a rule, bear a relation to the area of infarcted tissue. A small infarct will give slight albuminuria alone with a few erythrocytes; one of moderate size will give more definite findings, but a large one will frequently so disorganize the affected wedge of tissue that no excretion from it occurs and the urine may contain no evidence at all of disease—even red blood-cells being absent.

RENAL TUMOURS

Innocent renal tumours, with the exception of papillomata of the renal pelvis, are symptomless. The latter give rise to intermittent haematuria. The blood is well mixed with the urine. Clots, shaped to the ureter, may be found;

their passage is often painful. Albuminuria, except of a degree to be accounted for by the blood, does not occur, and casts and renal epithelial cells are not present. Renal function tests are normal.

Malignant renal tumours of whatever type may be accompanied by haematuria and anaemia.

In many cases **haematuria** is the earliest sign of disease, but in others, particularly children, blood may never appear in the urine. In those cases where it occurs the bleeding is at first slight, but, depending upon the type of destruction produced, it becomes gradually or rapidly more marked. Ureteric clots may be passed. Red cells may be found in the urine apart from grosser bleeding. Secondary infection is not uncommon, and, in this case, pyuria and bacteriuria are present.

Albuminuria, apart from bleeding, does not occur except to the extent of an occasional trace, unless there is pressure on the vena cava or renal vein. Casts are not generally found.

A secondary **anaemia** of the chlorotic type may be found. It is due to two causes, haematuria and cachexia. In the absence of a history of haematuria it may be taken, if present, as a measure of the extent to which the disease is affecting the general health. Absence of anaemia does not indicate necessarily a good immediate prognosis. Comparative readings will give more valuable information than will a single isolated determination.

RENAL TUBERCULOSIS

Tuberculous renal lesions are at first confined to the central part of the pyramids; as the area of caseation spreads, it ultimately becomes contiguous with the surface of the kidney pelvis. This results in a loading of the urine with cellular and caseous debris and with a constant pyuria. Should the local lesion involve blood-vessels of any size haemorrhage may occur. Tubercle bacilli are present, often in considerable numbers. Not infrequently, as in pulmonary tuberculosis, the lesion is also the site of secondary infection.

Urinary Findings

Considerable polyuria is frequent at an early stage. The urine is generally strongly acid. This property, together with pyuria and sterility, is very characteristic of tuberculous urine. Gonococcal infection of the urinary tract will also produce this combination unless special cultural methods are employed. Albumin is present, but only in proportion to the amount of blood; in the presence of pus alone there is generally only a trace.

Pyuria is considerable in most cases. It generally runs parallel with the size of the ulcerated surface.

Haemorrhage often occurs. This may be microscopical only, but, in such cases, there is generally to be discovered at some period of the disease a greater quantity. As in phthisis, its appearance is generally periodic.

Casts are not usually present.

Bacteriology

Great care must be taken, when examining urine for the tubercle bacillus, to avoid confusion between it and the smegma bacillus. Catheterization is the first precaution; the other is adequate decolorization by acid and alcohol. Guinea-pig inoculation provides the final proof. Should a number of apparently acid-fast bacilli be found with no other urinary abnormality, great suspicion should be aroused as to their non-tuberculous character.

It must be remembered that in small numbers tubercle bacilli can be regained from the urine in some cases of miliary tuberculosis and, possibly, also in widespread phthisis, signs of renal damage being absent.

Tuberculous disease of the urinary tract is frequently complicated by secondary infection. Therefore, the association of increased frequency of micturition together with pyuria and an obvious *Bacillus coli* infection must not necessarily be regarded as being a complete picture. Tuberculosis, so far from being necessarily excluded, is often to be included though latent.

The tubercle bacillus can either be looked for directly in the centrifugalized deposit of a twenty-four hour specimen

by the usual methods, or—a more accurate procedure—by the inoculation of such a deposit into two guinea-pigs. If two animals are used one can be killed after five weeks, with the chance of making an earlier diagnosis. The specimen for such a test must be collected in a sterile manner. A negative result does not exclude tuberculosis, but a positive one is the rule in all definite cases.

One final point is of considerable importance in estimating the value of the urinary findings. Owing to the caseous nature of the process it is not unusual for plugging of the ureter to occur from time to time. This may render the urine free of abnormalities for the period of obstruction. Whereas, however, a clearer urine without such plugging is often a sign of improvement and is associated with a diminution of fever, when plugging occurs a clearer urine may be associated with a slight change for the worse in the patient's general condition.

The other findings in renal tuberculosis are a secondary anaemia and, sometimes, a slight degree of leucocytosis.

CHAPTER XXIII

OTHER UROGENITAL DISEASES

BACILLUS COLI INFECTIONS

Acute Pyelitis is an acute inflammatory condition of the renal pelvis produced generally by *Bacillus coli*, occurring both in children and in adults. There is an acute swelling and hyperaemia of the renal pelvic mucosa, together with a profuse outpouring of polymorphonuclear cells. The mucosa is not, as a rule, exfoliated to any great extent. As a result of the acute inflammatory process numerous bacilli and polymorphonuclear cells appear in the urine. A drop placed directly upon a microscope slide and examined with the $\frac{1}{6}$th objective will show in one field one or more pus cells and many motile bacilli.

The urine is acid and generally contains a small quantity of albumin. It is mucinous in appearance and emits a typical 'fishy' smell. If the attack is severe a few red blood-cells may be found, and in much rarer cases there is frank haemorrhage. Casts are not present.

The picture is frequently complicated in children, and, less often so, in adults, by an obstruction to the ureteric lumen, presumably at the pelvic end, by the swollen and inflamed mucosa. Under these circumstances the pelvis forms an abscess cavity under tension, whence toxins and possibly bacteria escape into the blood-stream and give rise to severe symptoms. Rigors are common; indeed a rigor in a female child is always strongly suggestive of an acute pyelitis. The smaller size of the ureter may explain the commoner incidence in children of these acute symptoms.

Alkalinity of the urine, produced by potassium citrate or sodium bicarbonate, appears to coincide with a cessation of the fever; but should acidity return the fever and its accompaniments return with it. Thus, the treatment must be persisted in for a long period. The reason for this effect is obscure. The acute general symptoms are usually asso-

ciated with leucocytosis, and there is a reasonable possibility, on the analogy of infections by other members of the coli-typhoid group, that blood-cultures would in some cases be positive. Agglutinins are formed against the organisms, but only in very low dilution.

The Pathological Findings are, therefore, bacilluria, pyuria, sometimes slight haematuria, and a variable leucocytosis.

Where leucocytosis is high, and where symptoms—rigors and abdominal pain—are severe in an adult, the possibility of severe renal destruction, or even necrosis, necessitating immediate surgical intervention, should be borne in mind. In such a case blocking of the ureter by debris may deprive the urine of its pathological constituents, even rendering it sterile for a period. Apart from this, the amount of pyuria and of bacilluria runs parallel with the severity of the process.

Should casts be found in a case suggestive of acute pyelitis, the lesion has also involved the kidney and the condition is one of pyelonephritis. Acute pyelitis may be a determinate disease, but it often becomes chronic.

CHRONIC PYELITIS

The findings in chronic pyelitis are similar in kind to those present in the acute condition; they are bacilluria and pyuria. A small quantity of albumin may be present, and a slight leucocytosis may occur, but the count may be normal or there may even be a leucopenia.

In addition a secondary anaemia of the chlorotic type is common, the haemoglobin being sometimes very considerably reduced.

The urinary signs of the disease are, as a rule, constantly present, but vary greatly during the long course. This variation may be due to a true diminution or accentuation of the process, or it may be apparent only and the result of temporary ureteric obstruction. A bilateral lesion is the rule in chronic cases, but bilateral obstruction is uncommon. The symptoms of a chronic *B. coli* pyelitis may be superimposed upon an underlying tuberculous renal lesion. The

presence of the latter may be suggested by a rather more profuse haematuria. Less commonly *B. paratyphosus*, *B. proteus*, and similar bacteria are found.

B. COLI BACILLURIA

In many patients, who have harboured the bacillus for some considerable time, the urinary tract ceases to be reactive against the organism; and, though the latter may be present in quantity, there is no corresponding pyuria. A few polymorphonuclear or squamous cells may be found. The condition may or may not be preceded by a clinical pyelitis.

Vaccine Treatment

Unless all steps to eradicate any mechanical and structural causes of chronic pyelitis have been attempted, it is unlikely that vaccine treatment alone will be of much value. The more chronic the condition the more worthy are vaccines of a trial. They should be given in doses that will just produce a slight febrile reaction, and the size of the dose, where possible, should be increased up to 500 millions. The first dose must be small (five millions) and the intervals should be of about six days.

Should bacteriological examination of the urine drawn from both kidneys convict one organ only, pelvic lavage may be advisable.

Vaccine treatment of acute pyelitis is of no value.

ACUTE PYELONEPHRITIS

Acute pyelonephritis is a rare condition in which an acute pyelitis extends from the pelvis into the renal tissues. The pathological findings are those of an acute pyelitis with the following additions. Albuminuria is generally of a higher degree. Casts, chiefly epithelial, granular, and hyaline, are present.

CHRONIC PYELONEPHRITIS (Ascending Pyelonephritis)

This condition, formerly called the 'Surgical Kidney', results from an ascending infection from the bladder. Cystitis has generally resulted as a sequela of obstruction to bladder emptying, due to urethral stricture, enlarged

prostate, or some other cause. The ureters and renal pelvis also become dilated and their contents infected.

The Pathological Findings are therefore mainly those of the causative cystitis, the urine being offensive, sometimes ammoniacal, acid, or alkaline, according to the type of infection, containing much pus and a relatively small quantity of albumin, and being heavily infected. The commonest infective agents are *Bacillus coli*, *B. proteus*, the staphylococcus, and *Streptococcus faecalis*.

In addition to these urinary changes, casts—epithelial, granular, hyaline, or leucocytic—may be found, haematuria may occur, and the signs of renal inadequacy may be discovered. The earliest of these are a disturbance of Ambard's coefficient and a positive urea tolerance test; later the blood urea becomes raised, and the urea concentration and water tests show signs of diminished function. Owing to the frequency with which a latent form of the condition accompanies enlargement of the prostate, and because of the danger of subjecting uraemic patients to infection and operation, renal function tests should, as a routine, precede prostatectomy (see p. 316).

RENAL CALCULUS

Calculi may be formed in the renal pelvis and may exist in combination with or apart from infection. In the latter case the findings will be those of a pyelitis; haemorrhage may or may not be frequent. In the absence of pyelitis the pathological findings suggestive of renal calculus are: (i) the presence of certain crystals in quantity in the urine; (ii) evidence in the urine of persistent but mild trauma of the renal pelvis.

The crystals whose presence in quantity in the urine, in association with clinical signs and symptoms of calculus, is suggestive, are uric acid, calcium oxalate, and cystin.

Profuse haematuria may occasionally occur, but this is uncommon; far more frequently a few red blood-cells are seen in the urine microscopically. White blood-cells are generally present, casts are not found, a few pelvic epithelial cells are generally present.

PERINEPHRIC ABSCESS

Suppuration may arise in the perirenal tissues from a variety of causes. The commonest type is that seen in association with staphylococcal infection of the skin or of other parts of the body. Here the organism becomes localized in the perinephric tissues in one of two ways: either the site is peculiarly suitable culturally for the *Staphylococcus aureus*, or it is reached by direct extension from the superficial renal cortex; in each case the organism has probably been carried by the blood-stream. Some observers state that there is a slight staphylococcal cortical lesion in every case.

The Pathological Findings are of three types :

I. Urinary.
II. Haemic.
III. Of the Primary Infection.

Urine

In a large majority of cases the urine will be found to contain *Staphylococcus aureus* and, in association with this, a few red blood-cells and rather more leucocytes will be found. The urine should be collected aseptically.

Blood

A leucocytosis is present varying from 12,000 to 30,000. This, in cases where the patient's resistance is good, will vary directly with the latter and with the activity of the infection. Where the resistance is poor the figure may be lower.

Of the Primary Focus

Careful examination of the skin, nose, bones, and other areas that are sites of election of the staphylococcus may reveal a local inflammatory condition. The organism should be isolated carefully from this by smearing some of the pus aseptically upon an agar slope, or from the urine, in order that a vaccine may be made. This, after complete surgical drainage of the foci, both primary and renal, may be of use in helping to hasten recovery.

Other types of perinephric abscess are those secondary to a pyelonephritis, pyonephrosis, or other renal suppurative conditions, and those secondary to gross sepsis in the peritoneal cavity or pelvis, such as a suppurative appendicitis or oöphoritis. Here the pathological findings will be those of severe sepsis, high leucocytosis, and considerable secondary anaemia, combined possibly with slight urinary changes similar to those described in the staphylococcal condition. The organism present will vary with the cause.

In both types aspiration of the abscess will yield pus containing polymorphonuclear cells, cellular debris, and the causative organism. Smears as well as cultures should be made.

ABNORMALITIES OF THE URINE

Normally excreted urine may vary in the amounts of its normal constituents, or it may contain in it substances whose presence is abnormal. In either case the method and manner of excretion is normal, the kidneys not being diseased.

Quantity

The normal quantity for twenty-four hours is between 1,200–1,500 c.cm. in most adults, but varies with the weight. Adults generally pass about 1 c.cm. per kilo per hour. In children the amount is more, about 4 c.cm. per kilo per hour. At night the amount excreted is normally much less. Nycturia, or a condition where the night output exceeds that of the day, is found in oedematous conditions, whether of cardiac, renal, or hepatic origin. The first of the three is the commonest cause.

Polyuria

The urine is increased where the fluid intake is raised; where the rate of blood-flow through the kidney is increased, as in hypertension and recovery after heart failure; where there is a hydraemia, as in diabetes mellitus; where renal permeability is increased, as in pituitary lesions. Certain drugs, such as caffeine and theobromine, have a direct renal diuretic effect. Novasurol used in conjunction with am-

monium chloride produces diuresis by enabling the body tissues to remove oedema fluid.

Oliguria

The output of urine is less during heart failure, during acute or severe nephritis, during fevers, and when the body has lost much fluid from other causes, such as hot weather, severe haemorrhage, an attack of diarrhoea, or when the blood-pressure falls and remains low as in shock.

Appearance

Normal urine should be clear. A meal rich in vegetable food may cause slight cloudiness due to phosphates in urine passed soon after. The normal colour varies with the specific gravity, being lighter with the lower figures.

Coloration due to Disease

Pale

The urine is abnormally pale in non-haemolytic anaemias, in chronic nephritis, in amyloid disease, and in diabetes mellitus, and darker than normal in febrile conditions and where there is an increased haemolysis. The colour is generally due to urochrome and uroerythrin.

Yellow

The urine is abnormally yellow in slight obstructive and in non-obstructive jaundice, owing to the presence of bile pigment. Where the latter is present in quantity the foam caused by shaking will be shown to be yellow.

Bile, according to its quantity, will colour the urine deep yellow, green, brown, or nearly black. Bile salts, if in sufficient concentration, are detectable by Hay's flowers of sulphur test. Bile pigment, chiefly bilirubin, is generally proved present by Gmelin's test.

Brown or Red

Blood in quantity will colour the urine red. In lesser amount, where the rate of bleeding is slow enough to allow of reduction to methaemoglobin, the colour becomes brown. The same rule applies to haemoglobinuria. The microscope is the only safe and definite test for blood in the urine.

Haemoglobinuria occurs where, as a result of the lysis of erythrocytes, haemoglobin in sufficient amount is set free in the blood. The commoner causes of this are poisons —snake venom, chloroform, phosphorus, or haemolytic antibodies, as are present in paroxysmal haemoglobinuria, in Raynaud's disease, or syphilis, and occasionally after a transfusion. In blackwater fever methaemoglobin is chiefly present. Should the quantity of free haemoglobin present in the blood be below a certain amount, the reticulo-endothelial system is competent to absorb it, and the only change, if any, will be an increase in the amount of urobilin present in the urine.

The tests for haemoglobinuria and methaemoglobinuria are spectroscopic. The presence of these bodies may be suspected where, in spite of a definitely bloody appearance of the urine, no, or very few, red blood-cells are found in it microscopically. Centrifugalization will cause no clearing of colour from the supernatant level of the specimen in haemoglobinuria. In haematuria the red blood-cells are, of course, thrown down. It must be remembered that blood will become lysed in urine and that deductions can only clearly be drawn from a freshly passed specimen. Albuminuria of an equivalent degree coexists.

In paroxysmal haemoglobinuria the condition will be brought on after immersion of a hand for a few minutes in a basin of cold water.

Urobilinuria. Normally blood-pigment is converted into bilirubin, which is excreted in the bile; the intestinal organisms convert most of this into urobilin, some of which is reabsorbed and destroyed by the liver. Urobilinuria is common in fever and in hepatic disease, and has been observed in pernicious anaemia and in chronic malaria, and when blood has been effused in quantity into the body tissues.

Black

The urine of some patients who have melanotic growths, though generally clear after being passed, becomes black on standing, or on the addition of a few drops of ferric chloride. The same colour changes occur in alkaptonuria.

Coloration due to Drugs

Black

The absorption of carbolic acid, creosote, resorcin, and other coal-tar preparations may lead to the excretion of pyrocatechin and hydroquinone, and, therefore, of dark, even black, urine. The blackness is accentuated by standing.

Red

Haematoporphyrinuria, giving a 'port-wine' coloured urine, may be produced by trional, sulphonal, and tetronal. Antipyrin and pyramidon also may produce a red colour.

Chrysarobin, senna, rhubarb, and santonin give rise to the excretion of chrysophanic acid, which turns reddish in the presence of alkali.

Blue

Methylene blue may give a blue or a green colour to urine if absorbed in sufficient quantity.

Deposit

The commonest macroscopic urinary deposits are mucin, phosphates, urates, pus, and blood. The semi-translucent nubecula common in normal urines on standing is formed of mucin.

Phosphaturia

Phosphates form a prominent urinary constituent of the urine in two conditions. Freshly passed alkaline urine may contain an undissolved cloud of phosphates soluble on the addition of a few drops of dilute acetic acid, or the cloud may only appear after heating. This condition is essentially merely a manifestation of the alkalinity of the urine. Magnesium-ammonium phosphates occur in the form of 'coffin-lid' crystals in ammoniacal urinary decomposition.

Uric acid crystals are not a very common urinary sediment. They are found when the urine is very acid or very concentrated. Other factors contributing to the possibility of their presence are those accompanying nucleo-protein break-down, either exogenous, as when sweetbread, liver,

kidney, or brains have been eaten, or endogenous, as in leukaemia or acute febrile conditions. Uric acid calculi are usually brownish yellow, hard, of uneven surface, and laminated on section.

Urates

Sodium acid urate forms the 'red pepper' or 'red brick-dust' granules present after urine has become cool. Urates dissolve on heating.

Oxalates

Calcium oxalate is found in either acid urine, generally with urates, or alkaline urine, generally with phosphates. Certain foods increase the oxalate output; among these are tomatoes, rhubarb, strawberries, and spinach.

Neurasthenia is not infrequently associated with oxaluria. It should be remembered that oxalate crystals in the urine, in association with the other clinical and pathological signs of renal calculus, are additional evidence of the condition.

Leucin and tyrosin crystals are present in some cases of acute yellow atrophy.

Odour

The urinary odours most commonly detected are the ammoniacal odour characteristic of considerable bacterial decomposition in the bladder, and the fishy, 'haddocky' odour of urine infected with *Bacillus coli*. Drugs such as turpentine, menthol, cubebs, copaiba, and sandal-wood oil produce smells that are characteristic. Coffee and asparagus also give odours to the urine.

URINARY CONSTITUENTS DISCOVERABLE ON ANALYSIS

Inorganic

Certain variations occurring in the inorganic urinary constituents are of clinical significance.

The chlorides in the urine are decreased in renal disease; in acute febrile disorders, typically in pneumonia; and in cases where vomiting or diarrhoea is excessive.

The second example is probably a latent manifestation of the first, the circulating toxin causing sluggishness of function and even microscopical changes such as cloudy swelling or hyaline degeneration in the renal cells. This runs parallel with the fact that a persistent or progressively increasing retention of chlorides in pneumonia coexists with a severe and often fatal attack. The urinary chloride diminution in vomiting and diarrhoea is explained by the abnormal loss of the salt by mouth and rectum.

Phosphates are occasionally present in large amount in the urine of individuals suffering from rather indefinite symptoms, as lassitude, thirst, headache. Administration of an acid mixture is often followed by a disappearance of both phosphaturia and symptoms.

The ethereal sulphates are said to vary directly with the amount of putrefaction present in the bowel; this is probably true of indican. This substance may be increased by a meat diet, and also in conditions such as empyema or subacute otitis media where protein decomposition is occurring.

Cystinuria is a congenital disorder of amino-acid metabolism, often familial. The importance of its recognition is in the fact that cystin calculi are not uncommonly associated with it.

The nitrogen content of the urine, after eliminating or making allowance for that of the food, runs parallel with the extent of body metabolism. It is increased in all conditions of increased metabolic rate, as in exercise, fever, Graves's disease, and diabetes.

The ratio of ammonia to urea in the urine is a measure, in the absence of ammoniacal decomposition, of the extent of an acidosis. In diabetes, for example, the extent to which ammonia is called upon to fix acid bodies may be measured by determination of the ammonia.

Organic

The commoner organic urinary constituents are glucose, lactose, urea, aceto-acetic acid, β-hydroxybutyric acid, and the more complex bodies—albumin, globulin, and Bence Jones' protein.

Glucose is present in detectable amounts in true diabetes and in certain other conditions. This second group comprises alimentary glycosuria, glycosuria due to cerebral, pancreatic, supra-renal, pituitary, and thyroid causes.

Most normal individuals can assimilate 100 grammes of glucose upon an empty stomach without manifesting glycosuria; a much larger quantity of the more slowly digested carbohydrates can be taken. A positive result in the latter case is highly suggestive of diabetes mellitus.

Cerebral lesions, particularly near the fourth ventricle, may produce well-marked glycosuria. Examples are cerebral tumour, cerebral haemorrhage, and acute encephalitis. Another cause is hyperactivity or irritation of the anterior lobe of the pituitary body. This may occur in connexion with tumours, with chronic meningitis, usually syphilitic, or with haemorrhage. In these nervous conditions there is no accompanying acidosis (see p. 328).

Gross disorders of the pancreas, particularly acute pancreatitis and pancreatic tumours, are not infrequently causes of glycosuria (see p. 210).

The term **albuminuria** is generally rather loosely used. The substances present are serum albumin and serum globulin—a mixture of euglobulin and pseudo-globulin—either together or separately. True albuminuria is practically always accompanied by globulinuria.

The causes of albuminuria, apart from definite nephritic lesions, are excessive exercise, prolonged standing, and exposure to cold. The condition also occurs in adolescents and children as orthostatic albuminuria. In all of these cases globulin is usually a prominent constituent, and in none of them, apart from the occurrence of a few granular and hyaline casts, is any other symptom or sign of nephritis present. The so-called 'leaky kidney' is generally an organ in which previous disease or present arteriosclerotic scarring has left a local injury with no impairment of the general function; here also the globulin percentage tends to be higher than in the course of a definite chronic nephritis.

ORTHOSTATIC ALBUMINURIA

In orthostatic albuminuria the protein, often largely globulin, is absent in the specimen passed before rising in the morning, but present after the patient has been standing. All cases, particularly in the face of a history of scarlet fever, frequent tonsillitis, or other suspicious aetiological factors, need thorough investigation before they can be safely labelled 'functional'. The presence of red or white blood-cells, of casts other than hyaline, and of cardiovascular changes, or of evidence of inefficient renal function, must be excluded. Oxaluria is not infrequent. The condition is usually coterminous with adolescence.

FEBRILE ALBUMINURIA

Albumin is found frequently in febrile disorders. The associated toxaemia is probably more accountable for the condition than are the few degrees of added heat. The cause is to be found in the effect of the toxin upon the renal epithelium. Careful watching of the condition will give some guide as to the progress of the toxaemia. The percentage can only be accurately obtained from a twenty-four hours' specimen.

Congestive albuminuria has been described earlier (see p. 296).

Bence Jones' protein is found almost exclusively in myelomatosis, though examples have been recorded in cases of leukaemia and in secondary carcinoma of bone. A precipitate appears on heating to about 60° C.; it is non-soluble in acetic acid and redissolves partially or completely on further heating to reappear on cooling.

DISEASES OF THE BLADDER

CYSTITIS

Cystitis is generally the result of severe continued infection or of infection associated with some obstruction to the complete periodic emptying of the bladder.

Acute cystitis is most commonly caused by the colon bacillus; chronic cystitis by the staphylococcus, *B. proteus*, or the tubercle bacillus.

ACUTE CYSTITIS

The findings are:

I. Acute Inflammation of the Bladder Mucosa.
II. The Presence of the Infecting Organism.

Urine

The urine is, as a rule, acid in reaction. Blood in acute cases is present. It is red in colour and often most marked in the last urine to be voided. Clots may be present. Continued severe bleeding from the bladder is always suggestive of papilloma, carcinoma, vesical calculus, or tuberculosis.

The amount of albumin is small; the less the quantity the greater, in the presence of pus, is the probability of cystitis. The amount of albumin in pyelitis is intermediate between that of cystitis and nephritis. Polymorphonuclear cells are present in very large numbers. In the more chronic cases where ammoniacal decomposition is present, they, together with the considerable amount of secreted mucin, often form a ropy, mucinous, sometimes almost gelatinous mixture. In addition there is often an opaque greyish deposit of pus. Desquamated bladder epithelium is always to be found microscopically; the cells occur in smaller groups than do those of renal pelvic epithelium.

The *Bacillus coli* is the commonest cause. *B. typhosus*, the pneumococcus, and the streptococcus of erysipelas are also causes of acute cystitis complicating typhoid fever, pneumonia, and erysipelas.

Vaccine treatment is disappointing in both acute and chronic cystitis.

Blood

A leucocytosis is usual.

CHRONIC CYSTITIS

The urine is frequently alkaline and smelling of ammonia. The albumin is similar in quantity to that found in the acute condition. Blood is present in lesser quantity and is often only microscopically detectable. Ammoniacal

decomposition, with the associated destruction of cellular outline and the presence of ropy masses, is far commoner. Phosphatic calculi are common. The infection is often a mixed one—staphylococci being frequently associated with *B. coli* or *B. proteus*.

Tuberculous cystitis is generally secondary to renal tuberculosis, the signs and symptoms of which are present also. The tubercle bacillus must be differentiated from the smegma bacillus, if necessary by animal experiment (see p. 299). Other organisms are often present and tend to mask the tuberculous picture.

GONORRHOEAL CYSTITIS

This may be pure or mixed. In the former case the urine has the cellular and albumin content of any form of cystitis, but is generally acid in reaction and without ropy masses. Owing to the cultural delicacy of the organism, the urine may be apparently sterile. These characteristics are also those of tuberculous cystitis, from which it must be differentiated. Gonococci are, as a rule, to be found in the prostatic secretion, with or without prostatic massage; they may be distinguishable in the urinary pus, especially in prostatic 'threads'. When other organisms are present the urine is frequently alkaline, ammoniacal, and sometimes contains 'ropy' pus; the gonococcus is not usually to be found. In these cases urethral discharge and the results of prostatic massage are the only diagnostic hopes. Where the gonorrhoeal infection is pure, vaccines may be worth a trial; in mixed urinary infections they have little value.

In cases of cystitis, of whatever cause, the urine should be examined as soon after being passed as is possible, for the cellular morphology is quickly destroyed by the bacilli present.

STONE IN THE BLADDER

Haematuria is the only finding characteristic of vesical calculus. It may occur in the form of fairly continuous microscopic amounts, or in occasional larger quantities.

Cystitis, generally of a severe and acute variety, may coexist.

NEW GROWTH OF THE BLADDER

The commonest types of new growth occurring in the bladder are papilloma and carcinoma.

In the early stages of either haematuria, microscopic or gross, is usually the only sign. Later small masses of tissue may be passed, histological examination of which is valuable, provided that necrotic changes are not present. Moreover there may be superadded the signs of a chronic cystitis, for, particularly in the malignant cases, secondary infection is frequent.

DISEASES OF THE MALE GENITALIA

PROSTATITIS

The commonest cause of prostatitis is gonorrhoea. In the acute stage the organisms may exist in the urethra and in the accompanying structures in pure culture. After the first few weeks the tendency for secondary infection to occur increases progressively. As in other situations, these more vigorous invaders, generally staphylococci, streptococci, and diphtheroid bacilli, tend to oust the original infection. At the end of eighteen months the infection is almost always mixed, and by the end of three years gonococci have as a rule vanished.

The method of obtaining evidence as to the presence of a prostatitis is prostatic massage preceded by ureteral lavage.

RENAL FUNCTION TESTS BEFORE PROSTATECTOMY

Prostatectomy is performed under two conditions. Either the patient's early symptoms bring him for examination before there is any detectable impairment of renal function, or he comes for treatment for some severe and sudden emergency, such as complete obstruction, severe cystitis, or an associated stone in the bladder. Certain of the second group of cases will need an immediate cystotomy in any case.

The problem as to the help to be obtained from renal function tests thus falls under a variety of heads. The

patient who comes with the earlier symptoms of enlarged prostate either has or has not a normal renal function. In the first case the prostatectomy can be proceeded with; in the second, provided that the prostatic enlargement is causing some retention of urine, it will be necessary first to attempt to improve the eliminating power of the kidneys. This object is best attained by doing a preliminary cystotomy. All 'back-pressure' effects will thus be eliminated and the renal condition is likely to be improved by the free drainage.

The second stage, that of prostatectomy, should be delayed until there is no further improvement in renal function.

A similar position holds with regard to the cases upon whom an emergency cystotomy has been performed.

The tests of greatest value are:

The blood urea test,
The urea tolerance test, and
The urea concentration test.

A comparison between the results of several readings will give the best idea as to the progress of the condition. The blood cholesterol value gives no certain help in prognosis.

URETHRITIS

Gonorrhoeal urethritis is accompanied by a urethral discharge containing polymorphonuclear cells and gonococci. The more acute the attack the greater is the amount of pus; the more chronic, the greater the frequency of urinary threads. Smears of the pus, if carefully stained and examined, are generally sufficient for diagnosis. If cultures are made they must be accompanied by all sterile precautions and be made upon appropriate media.

Other forms of urethritis occasionally occur. The diagnosis is made in an exactly similar manner.

In anterior urethritis the first urine passed will contain the majority of abnormal constituents; in posterior urethritis these are equally present in the second glass (three receptacles being used for one evacuation). If the act is then

stopped and the prostate massaged, this third final specimen will contain pus, cells, or organisms in greater quantity than the second.

STERILITY IN THE MALE

The pathological causes of sterility are to be found in abnormalities of the semen. Syphilitic orchitis or gonorrhoeal epididymitis may produce an aspermia or an azoöspermia; these do not usually follow vesiculitis or prostatitis.

When spermatozoa in the examined specimen are abundant in quantity, sterility is probably not due to their inadequacy, for in such cases some of them are nearly bound to be living and functional.

When the numbers are few, examination as to the motility of any individuals may be of use. If present, the semen is probably active; if absent, probably the reverse.

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G. METABOLIC DISEASES

XXIV. Diabetes and Glycosuria.

XXV. Gout.

XXVI. Diseases of the Thyroid.
Graves's Disease.
Toxic Adenoma.
Myxoedema.

CHAPTER XXIV

DIABETES MELLITUS

Diabetes mellitus can frequently be diagnosed and often treated with moderate success by clinical means alone; but some cases occur where the diagnosis can be made by laboratory methods only, and there are many others in which an exact assessment of both sugar tolerance and insulin requirement, periodically carried out, would add considerably to both comfort and length of life.

General Considerations

The functions of the pancreas can be divided under two heads: the acinous part secretes digestive ferments into the intestine, and the β-cells of the islands of Langerhans are intimately connected with sugar metabolism. An acute pancreatitis or an obstruction to the pancreatic duct usually affects the former to the greater degree, though a pancreatitis is not infrequently accompanied by a glycosuria. The islands of Langerhans do not appear to be directly attacked by any known acute infective agent, rather do they seem to become the victims of toxic degeneration, acute or chronic.

Not until about seven-eighths of the β-cells have been rendered inactive do the symptoms of diabetes appear. Even in cases where the onset of the disease is abrupt there is an absence of signs suggesting any causative infection. There is, however, some evidence to suggest that arteriosclerosis, by affecting the pancreatic vessels, may be an aetiological factor in a certain group of cases. But whatever the primary cause may be it should be remembered that, as two-thirds of renal substance and a very large fraction of hepatic tissue can be dispensed with without evidence of inadequacy, so in diabetes, at the moment of its earliest diagnosis, a great fraction of functioning island tissue is already irremediably lost.

Secondary infections play a very important role in the

course of an established diabetes. The commonest are: staphylococcal skin infections, pyorrhoea alveolaris, sinusitis, influenza, acute bronchitis, pneumonia, ischio-rectal abscess, and pulmonary tuberculosis. Not only do these conditions lower sugar tolerance during the attack, but a series of them may depress it slowly and progressively. It is also probably true that the majority of cases of coma owe their onset entirely to some such acute secondary infective factor. These infections should be accurately diagnosed and ruthlessly treated in a known diabetic, for the disease may be continually aggravated and successful treatment gravely impeded by a chronic infection which in a normal individual would be of no account.

The insufficiency of the natural supply of insulin produces an inability on the part of the tissues to utilize sugar, with the result that hyperglycaemia and glycosuria occur and bring about the main symptoms of the disease. This carbohydrate-using deficiency is also accompanied by an incomplete oxidation of fats and an accumulation in the blood-stream of the toxic aceto-acetic acid, which causes the main symptoms of diabetic coma; β-hydroxybutyric acid and acetone accompany it, but are probably far less toxic.

The Blood-sugar

The normal kidney excretes glucose when the concentration of this substance in the blood reaches a level of about 0·18 gramme per 100 c.cm. This renal threshold is very constant, though in certain conditions it appears to be altered. These are renal glycosuria, where the threshold is lower, and myxoedema and diabetes mellitus, where the threshold may be raised. In order that loss of sugar may not occur in normal people the threshold is placed above the highest blood-sugar point usually reached after a carbohydrate meal. The figures generally accepted for the normal fasting blood-sugar concentration are 0·08–0·12 gramme per 100 c.cm. This level appears to be kept constant by a dual mechanism. Insulin is normally present in sufficient amount to allow the muscles and other tissues to utilize

the sugar and to store it as glycogen. When the blood-sugar falls, a stimulus, possibly nervous and travelling via the splanchnic nerves and hepatic plexus, stimulates the suprarenals (1). Adrenalin has the function of transforming the hepatic glycogen into sugar which is set free in the blood-stream for general use (2). Thyroxin has the power of rendering the liver glycogen more easily mobilized by the suprarenals. It is probably an excessive activity of this function that produces glycosuria in hyperthyroidism. Since the tissues are unable to utilize the dextrose there will be a hyperglycaemia, which will be accentuated for a variable time after meals.

Thus the normal blood-sugar is kept accurately under control at its fixed level except for a transitory increase after meals. This is greatest, if the blood-sugar is estimated half-hourly, in the specimen taken thirty minutes after the meal; it does not reach 0·2, and is followed by a fall that is complete in two hours, and generally long before.

The fasting blood-sugar of a mild diabetic may be normal, but after a meal containing carbohydrates it is raised **to a higher level** and **for a longer period**, and the figure becomes maximal later than in a normal individual. Should the rise transcend the renal threshold of 0·18 glycosuria will result. The second of these criteria, the time taken for the return to the normal level, is the more important in diagnosis.

The blood-sugar in a more severe case of the disease is high even before a meal, and according to the relation between this and the renal threshold sugar will appear in the urine constantly or not. Here again the postprandial fall is delayed, the peak of the blood-sugar curve is higher, and the figure has not become maximal after half an hour. After 50 grammes of dextrose the rise should normally be maximal in this period; but to less than 0·19 gramme, and to less than 0·18 after an hour. By two hours it should have disappeared. During the test no glycosuria should occur.

The blood-sugar is tested by taking specimens of blood before and at half-hourly intervals after the ingestion, in the case of suspected mild diabetes, of 50 grammes of dex-

trose, and, in the case of diabetics, of a meal containing a known small quantity of carbohydrate.

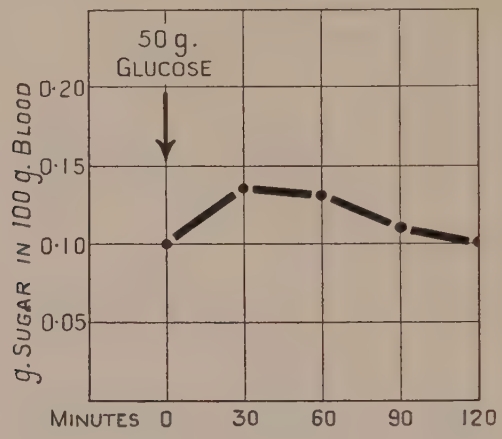

FIG. 3. Normal blood-sugar tolerance curve.

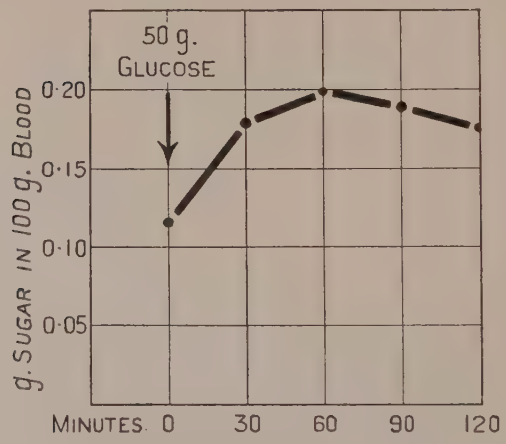

FIG. 4. Blood-sugar tolerance curve in mild diabetes.

DIAGNOSIS

Patients passing a quantity of sugar in the urine, especially if acetone bodies are also present on a normal diet, need, as a rule, no further test for confirming the diagnosis.

Latent cases will have been discovered by the unexpected finding of a reducing substance in the urine. Fehling's solution may be reduced in urine by uric acid in quantity, creatinin, homogentisic acid, lactose, laevulose, hydroquinone, and glycuronic acid, as well as by glucose. But reduction by the first two substances can be eliminated by diluting the urine to a specific gravity of 1,015 before performing the test. The other substances are rarely present. Benedict's solution is reduced by homogentisic acid, glycu-

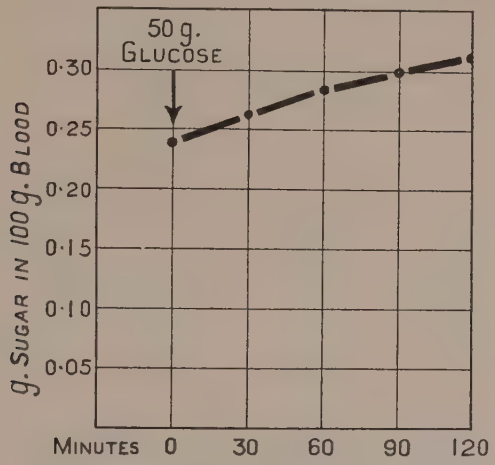

Fig. 5. Blood-sugar tolerance curve in severe diabetes.

ronic acid, and also by formaldehyde, which is sometimes added as a preservative. Glycuronic acid appears in the urine after the ingestion of chloral, chloroform, salicylate, aspirin, and turpentine. Here, as a rule, though the urine may turn green, no visible precipitate of copper settles out on standing. Nylander's reagent is reduced by none of these substances except pentose and glycuronic acid, but may be reduced by a great excess of urinary pigments. Lactosuria occurs in nursing mothers. Pentosuria is a pathological rarity, and is apparently an inborn defect occurring mostly in Jews. The presence of **aceto-acetic acid** in the urine of a diabetic indicates a carbohydrate-burning deficiency of an extent large enough to influence the oxida-

tion of fats. It is always associated with carbohydrate lack, as occurs also in starvation and prolonged vomiting. The ferric chloride test is of more practical value than is Rothera's test, as it is not so extremely delicate. A positive result is also given by salicylates, but the colour does not disappear on heating.

SLIGHT GLYCOSURIA

The causes of slight glycosuria are mild diabetes, 'alimentary glycosuria'—probably in some cases a euphemism for mild diabetes—suprarenal glycosuria, pituitary glycosuria, Graves's disease, and diabetes innocens. Other causes of glycosuria are dealt with on p. 312.

Mild Diabetes and 'Alimentary Glycosuria'

The blood-sugar curve is usually characteristic of diabetes and not conforming to the limits above described as normal. The most serious abnormality is a delayed rise and a delayed descent to normal. A blood-sugar curve which shows a rise to over 0·2 per cent. in thirty minutes, which is not maximal by thirty minutes and which has not fallen to normal by two hours, is diabetic in type. In case of doubt a second test should be performed after three months, and the sugar tolerance of the two compared. The fasting value may be normal in mild diabetes. True alimentary glycosuria occurs in some people. As a result possibly of a rather slow mobilization of insulin the blood-sugar rises rapidly after a meal to well over the threshold, 0·3 not being an unusual figure, and transitory glycosuria occurs. The fall is equally rapid and is down to nearly the previous level within an hour in many cases, and within an hour and a half in all cases. This gives a curve of the so-called steeple type, and is of no pathological significance. The rapid fall here contrasts with the slow fall of the diabetic curve.

Suprarenal Glycosuria

Nervousness, anxiety, and fright may all cause a temporary over-activity of the suprarenals. This, in the case of a medical examination, particularly in the case of young

adults, may mobilize enough sugar from the hepatic glycogen to cause a transient glycosuria. In such cases the fasting blood-sugar at a first examination may be high, but the shape of a curve after 50 grammes of dextrose is normal, its maximum is reached by the end of half an hour, and its fall to the fasting figure is complete in one and a half or two hours. Moreover, the fasting figures at subsequent examinations become less with the return of confidence.

Thyroid Disease

Both hyper- and hypo-thyroidism are not infrequently accompanied by hyperglycaemia. In myxoedema this is especially true after prolonged thyroid treatment. Thyroxin appears to have an effect auxiliary to that of adrenalin, by which the liver glycogen is rendered more available for mobilization as sugar. The blood-sugar curves in both cases resemble those of mild cases of diabetes. The chief difference between the hyperglycaemia of hyper- and hypo-thyroidism is that the latter condition is often accompanied by a raised threshold, so that glycosuria is therefore less common.

Pituitary Disease

In the hyperactivity of the anterior lobe of the pituitary body, particularly in developing acromegaly, glycosuria may occur. The fasting blood-sugar is rarely raised above normal. The blood-sugar curve is not characteristic.

Lactation

The sugar present in the urine of nursing mothers is most commonly lactose. The blood-sugar of the glucose tolerance test is, in shape and duration, of the normal type. It must be remembered that true diabetes may appear at this time.

Renal Glycosuria

Renal glycosuria is due to the presence of a lowered renal threshold for sugar. The characteristics are briefly: that the blood-sugar curves after 50 grammes of dextrose are normal in shape and dimension, that the amount of sugar in the urine is generally small and does not bear a definite relation

to the carbohydrate intake or to fasting, that no acetone bodies are present on a normal diet, and that in some of the cases albuminuria is also present.

In cases of doubt blood-sugar curves should be taken at two-months' interval and compared; the question is sometimes difficult to decide, and the opinion of an expert in such matters is desirable (3).

Nephritis

Towards the end stages of a chronic nephritis a raised blood-sugar may occur, especially in association with uraemia.

DIABETIC COMA

The Laboratory Findings in diabetic coma are:

I. The Presence of Gross Glycosuria.
II. The Presence of Aceto-acetic Acid and other Acetone Bodies in the Urine.
III. A much Raised Blood-sugar.
IV. A lower CO_2 Content in the Alveolar Air and Blood.
V. A Disturbance of the Urinary Ammonia-Nitrogen Ratio. Normally the percentage of urinary nitrogen in the form of ammonia is 2–5 per cent., in diabetic acidosis it may reach 10–25 per cent.

The typical clinical picture when combined with the first two of these is conclusive in nearly all cases.

Differential Diagnosis of Diabetic Coma

There remains for discussion a group of non-diabetic cases in which, besides coma, glycosuria of a definite degree is present. Here, especially if deprivation of food has produced a slight acidosis, mistakes are possible. The commoner causes of this syndrome are acute encephalitis, tuberculous meningitis, cerebral haemorrhage (or haemorrhage into a tumour) in the neighbourhood of the fourth ventricle, and uraemia. Should coma with glycosuria exist in the absence of aceto-acetic acid and acetone in the urine, one of these causes is probably present. Indeed, the absence of aceto-acetic acid and acetone bodies in a comatose patient

proves that diabetes is not the cause of the coma. The amount of sugar found, e.g. in encephalitis lethargica, may be enough to produce a rapid and marked reduction of Benedict's or of Fehling's solution.

A raised blood urea, to the content of about 100 mg. per cent., is not uncommon in severe diabetes, and is in acute cases partially due to water depletion, but such a figure is too low for uraemic coma. It should be remembered that renal disease is occasionally accompanied by a renal glycosuria, non-diabetic and of small amount. Valuable help in the diagnosis of uraemic coma can be obtained sometimes from the diazo reaction (see p. 277). An examination of the cerebro-spinal fluid may distinguish between tuberculous meningitis, encephalitis, and cerebral haemorrhage. The clinical findings in such cases are generally of greater value than are the pathological in arriving at a correct diagnosis.

Coma without glycosuria may occur in diabetes as a result of hypoglycaemia following the injection of insulin.

Prognosis

The present state, in any case of diabetes, can be accurately gauged by estimating the blood-sugar before and after a test meal of dextrose or after a known amount of carbohydrate. The degree of severity of the damage to the β-cells is directly proportional to the amount by which the curve transcends the normal or is delayed beyond it, as regards the attainment of its peak and the duration above the resting level.

The rapidity of advance or the stationary character of the lesion can be measured by comparing curves made at fixed intervals of time. Every diabetic should ideally be investigated periodically from this point of view. But it should be remembered in this connexion that any secondary infection, of however slight a severity, such as a cold in the head, pyorrhoea, or a boil, will vitiate the comparative value of such figures by causing a definite temporary diminution in sugar tolerance. The patient should therefore be enjoying his usual health at the time of such estimations.

Apart from comparative deductions it may be said briefly that a diabetic whose fasting blood-sugar is normal has only a slight lesion, and one that should be easily controlled; and that a diabetic whose fasting blood-sugar is raised has a more severe deficiency. It is also probable that a high threshold in a diabetic is an indication of a more serious type of disease.

Treatment

The ideal of treatment is to maintain the blood-sugar, by means of diet and insulin, within normal limits. The reason is that an increase above this probably causes the remnant of β-cells, already numbering only an eighth of their original normal figure, to work at a strain. A dilated heart is not allowed to compete with the maximum load possible to it: some rest should also be allowed to the pancreas. In order to assess accurately the amount of insulin necessary for this object, when a certain diet is given, blood-sugar estimations are necessary at the onset of treatment. Glycosuria will indicate that a rise of above 0·18 has occurred, but, apart from this, periodic examinations of the blood to assess the position are desirable. In most cases the patient should be taught to gauge his position from day to day by testing his own urine for sugar. Benedict's solution is the best for this purpose and an evening specimen should be selected. His allowances of food and of insulin should be adjusted to keep this sugar-free.

For other and fuller details of treatment information must be sought in books proper to the subject.

Pathological Considerations in the Treatment of Coma

Only one clinical pathological investigation is essential to the treatment of coma by insulin, and that is the detection of sugar present in the urine. This should be investigated three-hourly, if necessary after catheterization, during the intensive dosage generally employed, for only in this way can enough and not too much insulin be given. Insulin need not be pushed when the urine has become sugar-free.

Doses of insulin are given six-hourly, for not until then has its maximum effect occurred. The amount varies according to the clinical condition, 50 units being a moderate dose in an uninvestigated case and 100 or even 200 units being often necessary in known severe cases. After a six-hours' interval the dose should be omitted, halved, repeated, or doubled according to the clinical state and according to whether the urine contains no sugar, less, or an equal amount. Dextrose is generally given at the same time, 1 gramme for each unit of insulin, or 2 ounces for 50 units. For details of treatment appropriate text-books should be consulted. Concentration upon the insulin and sugar aspects of the case should not be so extreme as to allow the patient to die of water depletion, shock, and heart failure.

Apart from the insulin and glucose treatment of cases of diabetic coma every effort should be made to discover the underlying, probably infective, cause, and to remove it with all speed. A very complete and intensive clinical examination should be immediately made to this end, bearing in mind the commoner causes above described.

A white blood count may be of use; a leucocytosis will suggest some hidden pyogenic cause, and a definite leucopenia may be present in influenza. A series of leucocyte counts may provide useful information. A blood-culture may give information of value as regards prognosis. The leucocyte count is not affected by the diabetic side of the picture, so far as is known.

CHAPTER XXV

GOUT

General Considerations

The clinical manifestations of gout appear to depend upon some abnormality in the metabolism of uric acid bodies. This abnormality is partially constitutional and possibly to some extent acquired, for whereas a family history of the condition is not uncommon, yet chronic poisoning by alcohol or by lead has been proved to be concerned in the process.

There are two distinct stages in the development of the disease: urates are increased in the blood, and these are later deposited in the tissues of the body.

Increased Blood Uric Acid.

Urates are increased in the blood in a number of non-gouty conditions; endogenous examples of this are leukocytosis, leukaemia, pernicious anaemia, and chronic nephritis with urea retention; exogenous examples occur from the ingestion of foods rich in nucleo-proteins like liver, kidneys, and sweetbread, or in caffeine-like bodies. In gout the circulating uric acid is probably in the form of sodium mono-urate.

A mechanism other than retention of uric acid in the body tissues is probably concerned in the actual production of an attack of acute gout, for cases have been described in which the blood uric acid was at that time not raised above normal limits; moreover, though gout has been described in leukaemia and in other conditions where the blood uric acid is constantly high, yet the incidence of the disease in these conditions is not above the normal average. The actual mechanism of the deposition of the salt in the cartilage, tendons, and subcutaneous tissues is unknown.

The attack of gout is produced by the reaction of the joint or local area against the presence of the precipitated salt. As the disease becomes more chronic this periodic reactivity

becomes less acute, and the clinical condition is more that of a chronic arthritis.

Pathological Findings

The chief clinical pathological findings in gout are:

I. Abnormalities in the Amount of Blood Uric Acid.
II. Abnormalities in the Amount of Urine Uric Acid.
III. Signs of an Associated Disease such as Renal Sclerosis or Plumbism.

I. The normal **blood uric acid** content is usually taken to be less than 3 mg. per 100 c.cm. of blood, though occasionally individuals are seen who with no obvious cause have higher figures. Also the figures vary slightly with the method of determination. In chronic gout, or in acute gout between attacks, the figure is frequently, though not invariably, raised above 3 mg. per cent. A higher figure than this is very suggestive of gout; the increase is, as a rule, less than 6 mg. per cent. On the other hand, a normal figure may be found, and does not eliminate the possibility of gout.

The attack is not typically preceded by an increase in the blood uric acid content in the large majority of cases, but higher figures are generally seen in the acute than in the chronic condition (4).

II. The **excretion of uric acid** in gouty patients is slightly abnormal. On a purin-free diet it is rather less than that which occurs in normal individuals, but otherwise lies within normal figures. For a few days before the attack the excretion is usually considerably diminished; with the commencement of the attack the output begins to increase, and for a few days it is maintained above normal, then falling to a normal level. The increased figure during the attack is apparently more constant than is the diminution beforehand. Samples of urine must, of course, be taken from a twenty-four hours' specimen of known volume.

The normal daily excretion in an adult upon an average diet varies between 0·2 and 1·5 grammes. Before the attack the quantity is usually below 0·4, and on the second or third day after may be 1·9 grammes or even more. Between the

attacks the level may be normal or slightly lower, occasionally falling to 0·1 to 0·2.

In leukaemia the daily excretion is very high and may average 10 grammes per diem.

Treatment

It was first shown by Nicolaier and Dorn (5) that atophan produced a transient increase in the uric acid excretion in gout, the blood uric acid falling and the urine uric acid rising. A similar action occurs after the administration of sodium salicylate and cincophen. The excreted uric acid probably comes chiefly from the tissue fluids and blood. Evidence that it comes from already deposited foci in the tissues is at present lacking.

CHAPTER XXVI

DISEASES OF THE THYROID GLAND

Basal Metabolism

The determination of the basal metabolism is the laboratory measure which gives most information in this group of diseases. The actual performance of the test must be carried through with considerable precautions if results of any real value are to be obtained, and the patient should be sent to an expert for the purpose. The precautions to be taken in arranging for the performance of the test are:

1. The patient should be placed upon a diet practically consisting of carbohydrates and containing very little nitrogen for two days beforehand. This ensures a standard respiratory quotient.
2. No food must have been taken for at least twelve hours before the test.
3. The patient should undergo no undue physical exertion in the twelve hours immediately preceding the test, and must remain absolutely quiet for three-quarters of an hour immediately before the test. It is thus ideal, though not absolutely essential, that a patient should have spent the previous night in bed in the building in which the test will be carried out.
4. Besides exercise and food the factor of apprehension or nervousness is likely to vitiate results. For this reason it is wise to make two determinations during the test, and to repeat this double determination upon the following day. Should the readings be equal within 5 per cent. or so the result is clear, but the first one or two may give figures raised artificially above those succeeding them. Such an increase is often a measure of the patient's nervousness and the first figures must be discounted.
5. Certain patients are likely to give unreliable figures;

the presence of cardiac or pulmonary dyspnoea results in the performance, at rest, of more work than normal and a raised metabolic rate.

6. There is somewhat contradictory evidence as to the effect of menstruation on basal metabolism. It is therefore desirable to choose the intermenstrual cycle where possible.

Normal Variation

Eggert Møller (6), in an excellent summary of the available literature, states: 'It is thus seen that the basal metabolism in normal persons can vary as much as about ±15 per cent. of its mean value. A thorough investigation of the results shows, however, that most of the values lie within ±5 per cent. This fact illustrates the necessity of repeated determinations which agree well with one another for diagnostic purposes.' The variations between readings taken on the same day is smaller, but cannot be entirely eliminated. The normal figures, using Krogh's method, can be taken as being between 90 per cent. and 110 per cent. Besides hyperthyroidism the basal metabolism is increased in undue nervousness, early tuberculosis, pernicious anaemia in proportion to the haemoglobin deficiency, leukaemia, diabetes, and in febrile conditions of all kinds.

GRAVES'S DISEASE

General Considerations

The basal metabolism is, as a rule, increased in active Graves's disease, and the extent of the increase is generally proportional to the severity of the disease. The increase can be as high as 190 per cent., the normal being 100 per cent. Møller points out that variations of a much smaller degree than this are more significant than they superficially seem. He argues that in the severest form of myxoedema figures less than 60 per cent. are not found, and that this may be taken as the absolute zero of the clinical basal metabolism determinations which must be assumed to correspond to the complete failure of the thyroid function. Normally, therefore, about 40 per cent. of the metabolism

is directly sustained by the thyroid. If, therefore, the basal metabolism rises proportionately to the strength of activity of the gland, a thyrogenic increase of the basal metabolism from 100 per cent. to 180 per cent. really signifies that the gland's function has increased threefold; with a basal metabolism of 120 per cent. it would be increased by 50 per cent., and with one of 70 per cent. it would have fallen to a quarter of its normal amount.

This emphasizes the great importance of accurate results, and the possibility of being seriously misled by inaccurate data.

Diagnosis

The diagnosis of Graves's disease is a clinical matter, and complete reliance cannot be placed on the basal metabolism results. Just as in some of the 'formes frustes' of the disease one of the four cardinal symptoms may be lacking, so the presence of a raised basal metabolism is not absolutely invariable. Means and Burgess (7) found that 300 cases of definite hyperthyroidism all had an increased metabolic rate, and that of 290 doubtful cases it was normal in 173, in 12 below 90 per cent., and in 105 above 110 per cent. Du Bois states that this method of examination 'gives the best index of the severity of the disease and of the effect of treatment', and that 'a few mild and several typical . . . cases . . . may be within the normal limits'. It is possible that for some of these cases with low figures a basal metabolism of 90 per cent. may be normal, in which case a rise of 20 per cent. might remain undetected.

It is, however, probably true that a raised metabolic rate, other definite signs of the disease being present, is strong positive confirmatory evidence; that a normal metabolic rate, unless most of the other signs of the disease are definitely present, is strongly against the diagnosis; also that an increase or diminution of the metabolic rate generally coincides with the degree of thyrotoxicity.

In certain cases of hyperthyroidism, in which cardiac symptoms predominate, a definitely raised metabolic rate may be of great diagnostic value (see p. 156).

The basal metabolism seems to be at its highest during the first year of the disease and then to fall to a slightly lower level, where it remains.

The symptoms found by Møller to run most nearly parallel with the basal metabolism were exophthalmos and increased sweat secretion.

Prognosis

Apart from the fact that the basal metabolic rate tends to be higher in the severer forms of the disease, no direct reliance can be placed upon it alone as a guide to the future course.

Death may occur from circulatory failure or from the onset of an acute thyrotoxic crisis without any premonitory rise in the basal metabolism.

Determinations are, however, of great value in enabling treatment to be more accurately adjusted to the needs of the patient.

Treatment

Patients with exophthalmic goitre are treated by resection of the gland, by X-rays and radium, by iodides and other drugs, and by rest and liberal feeding. In most cases a careful watch upon the clinical signs and symptoms gives the best indication as to the course of the disease; conversely it occasionally happens that operative intervention is necessitated in spite of an increase in thyroid intoxication. But there undoubtedly remain cases where regular determinations will define the progress of the disease in such a manner as to allow of the least possible operative risk. Moreover, the type of treatment depends upon the degree of severity of the individual case, and in this way also metabolic rate estimations are an additional help when taken in conjunction with the clinical findings.

In Møller's cases the symptoms first to disappear, with clinical improvement, were nervousness, palpitation, and increased sweating, whereas tremor, tachycardia, and an increased metabolic rate persisted.

A point of further interest is that, although he found

X-ray treatment a valuable therapeutic agent in the less severe cases, yet in the first week after such therapy there was a temporary accentuation of symptoms and an increase in the metabolic rate.

Other findings in Graves's disease are:

1. Increased excretion of urea.
2. Hyperglycaemia (see p. 327).

TOXIC ADENOMA

The teaching of the Mayo clinic has been that, whereas exophthalmic goitre is a dysthyroidism as well as a hypothyroidism, toxic adenoma of the thyroid produces a pure hyperthyroidism. This teaching is by no means generally accepted, though it is valuable as a working hypothesis and a stimulus to further work. Boothby (8), in a series of 70 cases of adenoma with hyperthyroidism, found an average basal metabolic rate of 135, this being a lower average than occurs in Graves's disease.

Apart from this there is no essential difference between the findings in Graves's disease and in toxic adenoma.

MYXOEDEMA

Diagnosis

The basal metabolic rate in hypothyroidism is no more a means of absolute diagnosis than it is in hyperthyroidism.

It is probably true that in most cases there is a decrease in metabolism, which is proportional in degree to the severity of the lesion. In doubtful cases a metabolic determination is generally of great value, for the presence of a lowered figure is strong evidence in favour of hypothyroidism.

In most cases hitherto published the figures lie between 60 per cent. and 90 per cent. according to the severity of the disease. They tend to be lowest in cases of cachexia strumipriva.

Møller found that a moderately diminished basal metabolism was not invariably accompanied by an increase in weight, but that when the metabolic figures were below 80 per cent. there was always 20 per cent. overweight. He

states that most symptoms vary with regard to their relationship with a decreased metabolic rate, but that if a definite myxoedematous skin thickening is present the diminution is generally below 85 per cent., as originally stated by Plummer.

Treatment

It is in the determination of the optimum dose of thyroxin or thyroid extract that the basal metabolism determination in myxoedema has its chief value. Møller is probably not overstating the position when he says, 'The estimation of the right dose of thyroid is so important to the patient, and basal metabolism determinations are such a help in this, that it is desirable that all these patients should be controlled by this method of investigation'. But it appears that the full rise in rate in most cases is not complete until from one to two months have passed. The basal metabolism should be kept at a level lying between 90 per cent. and 110 per cent., and figures just below rather than just above 100 per cent. should be arrived at. This is especially the case where morbus cordis, nervousness, digestive abnormalities, or glycosuria coexist. Conversely, in cases showing adiposity, mental dullness, or ichthyosis, doses producing a final level of between 100 and 110 per cent. can be tried.

The other important pathological findings in myxoedema are anaemia (see p. 118) and changes in the carbohydrate metabolism (see p. 327).

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H. ALLERGY AND ALLERGIC DISEASES

XXVII. ALLERGY AND ALLERGIC DISEASES

Anaphylaxis.
Hypersensitiveness.
The Diagnosis and Treatment of Allergic Disorders.
Hay-fever.
Asthma.
Serum Sickness.
Skin Disorders.
Alimentary Disorders.

CHAPTER XXVII

ALLERGY AND ALLERGIC DISEASES

Allergy may be defined as a state of hypersensitiveness to some foreign material. Contact with such a substance is without effect in normal people, but in the hypersensitive it induces a '*reaction*', the symptoms of which constitute the various maladies to be described in this section. A complete exposition of the theoretical aspects of this strange group of disorders is not possible here.[1] A brief account of the nature of Allergy, so far as we understand it, will be followed by a general consideration of diagnosis and treatment; certain allergic disorders will then be discussed in more detail from this point of view.

EXPERIMENTAL ANAPHYLAXIS IN ANIMALS

Injection of horse serum or other foreign protein into a guinea-pig renders the animal hypersensitive, so that a second injection of the same material produces a reaction which is severe or fatal within a few minutes. The following facts are established:

A relatively small dose of serum will sensitize; it need not be more than 0·004 c.cm.

No anaphylactic reaction occurs unless the second injection is given after an interval of ten days from the 'sensitizing injection'.

Once established, the hypersensitive condition is permanent; it is transmitted from mother to offspring, so that the latter will react to a first injection of serum. The reaction is specific, only the protein with which the animal was sensitized being capable of causing 'anaphylactic shock'.

Our knowledge of the mechanism of this phenomenon is incomplete in many places; the following is an outline of a hypothesis well established by experimental observation.

[1] For fuller information the reader is referred to *Allergy, Asthma, Hay Fever, &c.*, by W. W. Duke (Henry Kimpton, London, 2nd edition, 1927), and to *Allergic Diseases*, by W. Storm van Leeuwen (Lippincott, 1925).

During the ten-day interval necessary for the production of anaphylaxis, a specific precipitin to horse serum is formed by the guinea-pig. Anaphylactic shock following a second injection is due to the union of the serum injected with this specific antibody in the tissue cells of the animal, particularly in nerve-cells and in those of smooth muscle. There have been many speculations as to why the cell equilibrium should be thus upset by this antigen-antibody reaction.

A sensitive guinea-pig can be desensitized with ease and certainty. It will tolerate a lethal dose of the specific protein if it is first injected with a small fraction of this. Tolerance is established most rapidly by intravenous injection, so rapidly that a lethal dose given sufficiently slowly is often without effect—the animal is desensitized before the full dose is given. This condition of 'anti-anaphylaxis' does not last; sensitiveness returns in a few weeks.

The symptoms of anaphylactic shock in the guinea-pig are the same, whatever protein is used for the experiment. The animal dies in convulsions, asphyxiated by spasm of the smooth muscle of the bronchioles. Post mortem, the lungs are found bloodless and emphysematous.

HYPERSENSITIVENESS IN HUMAN BEINGS

Naturally occurring human hypersensitiveness has been known for centuries. A little over twenty years ago its possible relation to animal anaphylaxis was realized. The similarity of the constriction of the bronchi in asthma and that in animals dying of anaphylactic shock was observed, and the suggestion naturally followed that asthma was an anaphylactic phenomenon.

In this group of maladies there is a great resemblance in many ways to the phenomena of anaphylaxis; but there are also striking differences. For instance, human beings are sensitive spontaneously, and only rarely are they made sensitive by treatment with a foreign substance. An enormous number of patients have been given a second injection of horse serum for therapeutic purposes. Serious symptoms of collapse after administration of serum are

excessively rare, and most of these have occurred after a first injection, the patient being naturally hypersensitive. Animals can be sensitized only to proteins; human beings may be sensitive both to protein and to non-protein substances. It is easy to desensitize an anaphylactic guinea-pig, but extremely difficult to desensitize a naturally sensitive human being. These differences, and there are others, will show that hypersensitiveness in human beings may be essentially different from anaphylaxis in the experimental animal. Until we have fuller knowledge of the underlying pathological process, it is well to restrict the expression anaphylaxis to the experimental condition. 'Allergy' is a wider term; it includes anaphylaxis and all similar conditions of hypersensitiveness.

The symptoms of allergic reaction usually occur very soon after contact with the 'allergen' to which the patient is sensitive; the interval may be a few seconds only, but is often an hour or more. Patients sensitive to the same material react in very varying degree; the difference in the intensity of the symptoms in hay-fever will illustrate this. Rarely patients are found who are excessively sensitive. In them a reaction resembles the 'anaphylactic shock' of animals; they become collapsed, with fall of blood-pressure and of temperature; consciousness may be lost; there may be much oedema of the subcutaneous tissues and of the lungs, and the breathing may become asthmatic. This type of severe general reaction is not common. It may end fatally, but, if adrenalin is given subcutaneously in adequate amount, recovery is more common.

In general there are two types of allergic reaction. First, the reaction may take place only where contact occurs between the allergen and the tissues. Examples of this type of reaction are hay-fever, abdominal pain after certain foods, the wheals obtained by skin testing, and many cases of asthma. Secondly, after absorption of the allergen by the blood, a 'general reaction' may occur—that is, a reaction in tissues remote from the site of contact. Common symptoms of the general reaction are urticaria and other skin eruptions, joint pains, and oedema. Naturally, in very

sensitive patients, a severe contact reaction is often combined with mild general symptoms.

The symptoms of allergic reaction will be considered further in discussing the different allergic maladies individually.

THE DIAGNOSIS OF ALLERGIC DISORDERS

The diagnosis of such well-defined conditions as hay-fever and the typical attacks of 'true spasmodic asthma' needs no consideration here. But there are many disorders where we may be in doubt whether or not the symptoms are those of allergic reaction. Obscure attacks of 'indigestion'; recurrent eczematous eruptions; a condition we are pleased to call 'angioneurotic oedema'; recurrent cough, with some difficulty in breathing and the appearance of widespread râles in the chest; migraine; are these manifestations of allergic reaction? We must consider several sources of evidence.

In the first place the sudden appearance of symptoms such as lachrymation, rhinorrhoea, itching and oedema of the pharynx or glottis, 'asthmatic' breathing—that is, impeded inspiratory and expiratory movements, with widespread fine rhonchus audible in the chest, due to bronchial spasm and oedema of the mucous membrane—urticaria and severe degrees of oedema of the skin, will strongly suggest an allergic phenomenon, if no adequate cause is found on physical examination.

Secondly, the family history may be suggestive; for about one-half of all patients with allergic disorders will give evidence of the familial nature of their malady.

Thirdly, there is a therapeutic test of which more use might be made, especially in the atypical cases of asthma where the diagnosis is uncertain. This is the effect of adrenalin. Subcutaneous injection of $\frac{1}{2}$ c.cm. of 1 in 1,000 adrenalin will almost always abort an attack of asthma within fifteen minutes or less if given at the onset of symptoms. A striking and commonly observed feature is that a comparatively large dose, such as 1 c.cm., may be given during a severe attack without producing unpleasant symptoms, whereas at other times $\frac{1}{2}$ c.cm. or less may give rise

to tremor and make the patient feel sick and uncomfortable. Adrenalin is the most effective drug in all forms of allergic attacks.

Fourthly, it seems probable that the majority of allergic patients give a positive non-specific skin reaction to certain substances. Van Leeuwen has found that all allergics react to an extract of human dandruff, whereas normal people practically never react; and the great majority, he finds, are sensitive to tuberculin. But no such substance is as yet in general use as a diagnostic test to differentiate allergic patients from normal people.

Having decided that the patient's symptoms are manifestations of an allergic reaction, the next step will be an attempt to discover the specific allergen responsible. The substances to which human beings may be sensitive are so numerous that exact specific diagnosis is usually impossible. This is not so inimical to successful treatment as might be supposed, for the general nature and distribution of the allergen concerned is often discoverable. The search may be narrowed down, for example, to some component of some toilet preparation, or to something in the air of a particular place. A study of the literature reveals the enormous number of substances which have been found at one time or another to cause allergic attacks. The following are some of the more important of these possible allergens: pollen, particularly light, dry, wind-borne varieties; various plants, either the leaves or flowers, or dried grasses; perfumes; animal hair and dandruff; feathers; smoke of various kinds; dust; food-stuffs; drugs; material introduced by the bites of insects; therapeutic sera; bacteria; vegetable decomposition products present in the air at low altitudes, named by Professor van Leeuwen 'climatic allergens'. Faced with such a multitude of possibilities, we must proceed by some logical analytical method to arrive at anything approaching a specific diagnosis. Before the skin reactions are thought of, the patient's own observations should be carefully considered, for occasionally a clue can be obtained in this way. He may find, for example, that he suffers from asthma in one place only, being free from attacks elsewhere;

or that symptoms appear only after handling certain materials. Most often no useful information is obtained in this way, but should careful questioning elicit any suggestion as to the general nature of the allergen responsible, it is not often difficult to design experiments whereby the hypothesis may be tested. Duke points out that proof that the offending substance has been discovered is obtained only by establishing the following facts: (1) symptoms are relieved by removal of the suspected allergen; (2) symptoms reappear if during a well period the patient is brought into contact with the suspected allergen.

Skin Reactions in Allergy

The skin of an allergic patient usually reacts to an application of the substance to which he is sensitive. This fact has led to the use of skin tests for specific diagnosis. Unfortunately the reaction is not specific; only in rare instances do we find a patient reacting to the one substance to which he is clinically sensitive and to no other. Usually a skin reaction is obtained with a large number of substances. Moreover, the skin does not always give a positive reaction with the allergen which is causing symptoms.

Having in mind these facts, and the enormous number of substances which are possible allergens, the surprising thing is that skin tests are of any value at all. Indeed, some authorities deny them any value for specific diagnosis. Professor van Leeuwen, for instance, says, 'Intradermal skin reactions may serve to diagnose the allergic state, but not to make a specific diagnosis'. It is nevertheless true that occasionally the responsible allergen is found by skin tests; either because it is the only substance which gives a reaction, or more commonly because it gives a very much more intense reaction than other substances. We consider, then, that there is a definite use for skin tests: first and most important, as a help in deciding whether the patient suffers from an allergic disease or not; and secondly as an aid, though it be a very slender one, to specific diagnosis.

Two methods of applying the skin tests are used: the cutaneous or scratch method, and the intradermal method.

The scratch method is recommended; it is the simpler and is painless. The intradermal method is more sensitive, giving a larger number of positive reactions, and being therefore more difficult of interpretation.

The Technique of the Method is as follows:

1. Clean the skin of the arm with alcohol, and dry.

2. With a needle, or the point of a scalpel, scratch through the horny layer of the skin, not deep enough to draw blood, over a tiny area. One cut one-eighth of an inch long suffices, or several little abrasions running crosswise may be made.

3. To this abrasion apply the protein extract to be tested. 'Protein extracts' for diagnostic purposes may be bought from several commercial firms. An extract suitable for the purpose is, however, quite easy to prepare. The substances responsible for 'reaction' appear to be soluble in water or dilute alkaline fluid; as their nature is quite unknown it is best to use the simplest form of extract, without making any attempt at purification. To precipitate the proteins with alcohol, dry them, and redissolve, may be effective in many cases; but the possibility that the allergen, which may not be a protein at all, is lost in the process cannot be ignored. Until we know more of these substances, it is better to use a simple aqueous extract, or an extract in N/100 sodium hydroxide. This may be preserved with $\frac{1}{4}$ per cent. phenol. For sterility, extracts must be filtered through a Berkefeld filter. In some cases the fat must first be removed by extraction with ether. For exact details the reader is referred to the writings of Coca (1). Coca's fluid for the preparation of extracts has the following composition:

KH_2PO_4 . . .	0·036 gramme.
$Na_2HPO_412H_2O$ . .	0·143 ,,
NaCl . . .	0·5 ,,
Carbolic acid . .	0·4 ,,
Water . . .	100 c.cm.

4. A control test must be done in exactly the same way, using the vehicle, whatever this may be, without any protein.

As many abrasions are to be made as there are materials to be tested; this will not be more than about ten at one time. They should be made about one inch apart. The total number of possible allergens one might test is very great; in practice, therefore, groups of closely allied materials—for example, the hairs of various animals—are tested first; the several members of one or more groups can be tested later if thought desirable.

A positive reaction takes the form of a wheal, surrounded by an erythematous area; it may appear almost immediately. The arm is examined at the end of half an hour, the various tests being compared with one another and with the control.

THE TREATMENT OF ALLERGIC DISEASES

General Considerations

Adrenalin is the sheet anchor in the emergency treatment of any form of allergic attack; this need not concern us further here. The treatment of the allergic state, which aims at desensitization of the patient, is difficult and uncertain, but often highly successful. In the less common cases, where the allergen responsible for the malady has been found, two methods are available. First, it may be possible to avoid contact with this allergen. A patient sensitive to unknown particles in the air in the lowlands may be able to live in the mountains and remain free from symptoms. Long-continued avoidance of contact with allergen sometimes, though not always by any means, results in desensitization. Secondly, we may attempt desensitization by 'specific treatment'. This rests on a belief, or of the results of its application, that repeated injections of an allergen, beginning with minute quantities and very gradually increasing the dose, will ultimately so reduce sensitiveness that the patient may remain symptom-free. The exact mechanism of this partial desensitization is not by any means understood; this is to be expected while the nature of allergy itself remains obscure. The dosage has to be regulated with the utmost care; too high an initial dose may precipitate severe symptoms. The technique of the method will be

considered further in discussing the treatment of hay-fever and asthma.

In the majority of cases, where the specific cause remains unknown, 'non-specific treatment' only is available. Professor van Leeuwen is so impressed by the results of non-specific treatment that he applies it in all cases, whether the offending substance is known or not. Non-specific treatment is based on the experience that sensitiveness to a particular allergen may be diminished by treatment not only with this allergen, but also with any other substance to which the patient may be sensitive. If positive skin reactions are obtained with several different proteins, beneficial results may be expected by anti-allergic treatment with any of these. Van Leeuwen draws attention to the fact that nearly all allergics are hypersensitive to tuberculin, and that non-specific treatment with this allergen is therefore rational in nearly all cases.

The febrile reactions produced by injections of milk or peptone are sometimes temporarily beneficial to allergic patients. Such treatment is a different type of non-specific therapy; it is quite empirical, and no reasonable explanation of its action has been suggested.

Non-specific methods will be described in more detail in discussing the treatment of asthma.

THE COMMONER ALLERGIC MALADIES

HAY-FEVER

The symptoms of hay-fever are so well known that space need not be occupied by attempting to describe them. Blackley, a Manchester physician, was the first to recognize that this disorder is due to pollen. He himself suffered from hay-fever; he showed that he could produce the symptoms in himself by instilling pollen or pollen extracts into the nose, that cutaneous application of pollen gave a characteristic skin reaction, and that symptoms varied in intensity with the pollen content of the air. His results were published in 1873.

In England symptoms usually begin towards the end of May, that is, shortly after the beginning of the grass-pollen

season, and last until about the middle of July. The pollens responsible are those of the common grasses, particularly timothy grass and rye. In America there are late cases, which may show symptoms as late as September. These are caused by the pollen of weeds, especially golden rod. They appear to be uncommon in England.

The majority of hay-fever patients give a positive skin reaction with a large number of pollens. These reactions are never obtained in normal persons. In this test, then, we have a method of confirming the view that a seasonal rhinorrhoea is hay-fever; it is important to obtain this confirmation, for a bacterial infection may give somewhat similar symptoms. Further, it is believed that the pollen or pollens which give the most intense skin reactions are responsible for symptoms; in any case, to choose these for specific therapy gives the best results in practice. For the successful treatment of hay-fever it is wise to keep a stock of pollens of the common grasses, though armed only with the pollen of timothy grass one can obtain good results in most cases.

Pollen extracts for diagnosis and treatment may be bought from commercial firms. The following method of preparing an extract is recommended by Duke:

The extracting fluid is a mixture of glycerine 66 per cent. and Coca's solution; to 100 c.cm. of this fluid 5 grammes of pollen are added, and the mixture is kept for two to three days in the ice-box, being shaken repeatedly during this time. The suspension is centrifugalized clear, and the extract passed through a porcelain filter for sterility. This concentrated extract is kept in sterilized bottles in the ice-box, and dilutions are prepared as required, using the same vehicle as diluting fluid.

In the application of specific anti-allergic treatment to hay-fever there is no standard method. It is generally agreed that prophylactic treatment should be adopted if the patient consults us before the beginning of the pollen season. Formerly, prophylactic inoculations were begun early in the year, about February or March, and injections were given at weekly intervals up to the beginning of the

pollen season. Now the fashion is for an intensive course during the two to three weeks before the beginning of the pollen season, injections being given at short intervals.

To find a safe initial dose the following method may be adopted: Decimal dilutions of the stock extract are prepared, and an intracutaneous injection of each dilution is made; the lowest dilution which gives a positive skin reaction is noted, and 0·1 c.cm. of this dilution used as the first dose.

The injections may at first be given twice daily, the dose being doubled on each occasion; after the first few doses daily injections are given, and the increment of dose made less steep. This increment will vary in different patients, and is a matter for careful consideration. If a reaction occurs after any injection the next dose must on no account be increased; a diminution is called for if the reaction is at all marked. Pollen reactions may appear within a few minutes; if general symptoms occur $\frac{1}{2}$ c.cm. of adrenalin, 1 in 1,000, should be injected subcutaneously.

If it is thought desirable to continue treatment into the pollen season, the dosage must be considerably reduced. This applies also to treatment started for the first time when the hay-fever season has begun. The initial dose in these cases will be from one-fifth to one-tenth that which would be given for prophylactic purposes. Infinite care needs to be exercised to avoid severe reactions, by cautious increment of dose and spacing of successive doses.

The results of anti-allergic treatment in hay-fever depend largely on the experience of the inoculator and the care which he bestows on the details of the treatment. With the same judgement and care the response in different patients will vary greatly. Some patients are rapidly desensitized; others need treatment for two or more seasons before they gain relief. It is never safe to hold out the prospect of cure by treatment for one season only.

ASTHMA

In the diagnosis and treatment of asthma a thorough knowledge of allergic disorders is of great importance.

Though typical spasmodic asthma presents no difficulty in diagnosis, there are many instances, particularly in children, when recognition of the true nature of the disorder is less easy. In young children, when the malady begins before the age of about six years, attacks most commonly resemble acute bronchitis of sudden onset, and indeed are often diagnosed as such. In adults also, though less frequently, diagnosis may present some difficulty, for similar dyspnoea may be a symptom of chronic bronchitis and emphysema, and sometimes of pulmonary tuberculosis. It may be noted here that the sputum should be examined for tubercle bacilli in all cases of asthma.

Believing as we do that asthma is in the great majority, if not in all cases, an allergic manifestation, the importance of being able to diagnose the allergic state becomes obvious. The great majority of allergic patients give reactions against one or more of the common test substances in general use; chief of these are extracts of meat, fish, shell-fish, eggs, milk, beverages, cereals, animal hair, feathers, &c. The cutaneous reactions with a series of these common allergens may be tried. This usually tells whether or not the patient is of allergic strain, for the majority of such patients, and especially young patients, will react to one or more of these substances. The specific allergen responsible for the symptoms is occasionally detected in this way. There is perhaps about an equal chance of arriving at a specific diagnosis from a careful consideration of the patient's observations on the circumstances attending his attacks. Professor van Leeuwen finds that in 75 per cent. of asthmatics the offending substance is a climatic allergen, that is, a substance present in the air, either peculiar to the patient's house or present in the general atmosphere outside. This is the percentage of patients who, he found, became completely free from symptoms after sleeping for two or three nights in 'allergen-proof chambers'. These are small, air-tight chambers, erected in the patient's bedroom and ventilated by purified air. The object is to imitate the conditions of high mountain air known to be so beneficial to most asthmatics (2).

When consulted by patients with symptoms of asthma, we should first confirm the view that these are manifestations of allergic reaction. We should then make an effort to determine the specific allergen responsible. This will usually fail; but if the *materies morbi* should be found, two methods of treatment arise for consideration. First, it may be possible for the patient to avoid contact with this particular allergen; it may be an article of diet, animal hair, feathers, and so on. Secondly, specific desensitization by the method already described should be attempted. The initial dose of the extract is determined in the manner described for the specific treatment of hay fever. Successive doses are given, first at daily, then at two-day intervals, and with stronger doses at intervals of three to seven days. The dose is increased until the patient appears to be deriving benefit, when no further increase is made. The usual precautions must be observed if a reaction follows any dose.

In the great majority of patients the responsible allergen is not found; here again two lines of treatment are to be considered. The influence of habitat on most asthmatics is so striking that we may try to get our patient away from the climatic allergens, which are probably the offending substances, by advising a change of residence, if possible to a place of high altitude. As this is not often possible, we must fall back on non-specific treatment.

Professor van Leeuwen claims that with his tuberculin treatment 50 per cent. of asthmatics are completely or almost completely cured, while 25 to 30 per cent. are considerably improved. Dr. Nelson, in this country, has applied this treatment to a series of cases, and has obtained equally good results. The details of the method are as follows:

The possibility of active tuberculosis is first excluded. Old tuberculin is to be injected subcutaneously. The initial dose is judged by the intensity of the tuberculin skin reaction. If the patient shows a very intense reaction, the first injection may be 0·1 c.cm. of 1 in 1,000,000. With a moderate skin reaction 0·5 c.cm. of 1 in 1,000,000 is given; if the skin reaction is negative the first dose may be 0·1 c.cm.

of 1 in 100,000. Injections are then given twice a week, each dose being increased by 0·1 c.cm.; after a time the interval is increased to one week, and later two weeks. When symptoms disappear, or when a reaction occurs, no further increase in the dose is made. Treatment is continued for a year or longer.

'Protein shock' has been used in the treatment of asthma with varying results. The method is based on the observation that asthmatic symptoms often disappear during an intercurrent infection. An artificial febrile disturbance can be produced by injections of foreign substances such as milk, or peptone, or an emulsion of coliform organisms. At the height of the 'shock' the asthmatic symptoms may be greatly relieved; the relief is temporary only, and attacks will probably recur in a few weeks.

When the allergen concerned is thought to be an article of diet, success has been reported from administration of peptone by the mouth. The patient is given half a gramme of peptone three-quarters of an hour before each meal. Improvement, if it occurs, appears after a few days.

Asthma is frequently associated with respiratory infections. There is some reason to believe that in certain of these cases the substance to which the patient is sensitive is the protein of the infecting organism. Should a constant flora be present desensitization can reasonably be attempted by the injection of increasing doses of a vaccine, the initial injection being much smaller than that commonly used.

SERUM SICKNESS

A group of symptoms known as 'serum sickness' occurs in a large percentage of patients injected with therapeutic sera. This percentage varies with the amount of serum injected; it is relatively small when amounts of about 10 c.cm. are used, but is well over 50 per cent. with large quantities. Symptoms occur after first as well as after second injections of serum; but they are more likely to occur after second injections. We have already mentioned that the rare alarming reactions after the use of serum have usually followed first injections in patients naturally hypersensitive.

A number of cases are recorded where the injection of very small quantities of serum—for example, one minim intravenously—produced death or very alarming symptoms. Professor Dudgeon (3) records the case of a patient with horse asthma who developed severe shock after the subcutaneous injection of 0·25 c.cm. of serum. It probably happens very rarely that human beings are sensitized in the same way that animals can be sensitized experimentally.

The possibility of serum sickness should never deter a physician from using serum when it is indicated, for the disorder is never serious. Usually there is an interval of about ten days between the injection of serum and the symptoms; but after a second injection the interval is much shorter. The prominent symptoms are fever, a rash varying in type, often erythematous and urticarial, pain and tenderness in the joints, and oedema.

Whenever it is necessary to inject a patient with a therapeutic serum, it is wise to inquire for a history of allergic disorders—hay-fever, asthma, especially 'horse asthma', and so on. Patients who give such a history should first be tested for hypersensitiveness by an intracutaneous injection of 0·01 c.cm. of serum. If a positive reaction occurs, the serum should be given by Coca's method. Desensitization is far more difficult in naturally sensitive human beings than in the experimental anaphylactic animal. Coca's method in such cases is as follows:

0·1 c.cm. of serum is given subcutaneously; doses are then repeated at thirty-minute intervals, each time adding 0·1 c.cm., provided no reaction occurs; if any signs of a reaction appear, a much smaller dose is given at the next injection, and the ladder climbed again until the required amount has been given.

When there is no suggestion that the patient is hypersensitive to horse serum, it is not really essential to take any precautions against reaction, though for the patient's comfort the intravenous route will be avoided in all but the most urgent cases; and the smallest adequate amount of the most purified preparation will be given.

ALLERGIC SKIN DISORDERS

Certain skin disorders are undoubtedly manifestations of allergic reaction. The general reactions, which are not infrequently observed after injection of the specific allergen into a sensitive patient, are commonly associated with pruritus, erythema, or urticaria. This form of skin reaction occurs, too, after insect bites in sensitive people, or after the ingestion of a particular food. It is a conspicuous feature of serum sickness.

Urticaria, both in acute and chronic forms, probably belongs to the allergic group of disorders in the majority of cases. Very frequently some article of diet is responsible, and every effort should be made, by eliminating one food after another, to make a specific diagnosis. This disorder, it has been suggested, may also be the result of hypersensitiveness to physical agents, such as light, cold, and mechanical irritation; for an account of these interesting cases the reader is referred to Duke's work.

Many cases of chronic eczema come within this group of disorders; the patient's skin is hypersensitive to some substance with which it comes in contact, which is without effect on a normal skin. Braun has successfully desensitized patients in whom a bee sting had produced very severe respiratory and urticarial symptoms, by using an emulsion made from the poison.

ALLERGIC ALIMENTARY DISORDERS

Allergy accounts for some obscure attacks of abdominal pain, associated perhaps with diarrhoea and vomiting. The diagnosis is usually made either from the patient's observations or by careful dietary experiments. Skin tests are of particularly little value for specific diagnosis in the food-sensitive cases. Such patients, as a rule, give positive reactions with so large a number of foods that no reliable conclusion, other than that hypersensitiveness exists, can be drawn.

It may be that other disorders, at present of obscure origin, will one day be shown to be manifestations of this

interesting and still little understood pathological process. Bacterial allergy has not been mentioned except in connexion with asthma. Bacteria are undoubtedly capable of acting as allergens, and some of the symptoms of infection may prove to be the results of allergic reaction. More fundamental work on the nature of allergy is needed. Too often it is regarded as one of the unimportant frills of medicine, whereas it may prove to elucidate much that is obscure about infection and immunity.

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APPENDIX

COLLECTION OF PATHOLOGICAL MATERIAL

BLOOD

Blood for Widal and Wassermann Tests, and for the van den Bergh and Andrewes Diazo Reactions.

Technique of Venepuncture.

Blood for Blood Urea and Blood Sugar Estimations.

Blood-culture.

Blood-count.

Blood for Fragility, Coagulation Time, Blood Platelet, Red Cell, and Reticulocyte Counts.

The Technique of Haemoglobin Estimations and Leucocyte Counts.

THE FRACTIONAL TEST MEAL

FAECES

General Examination.

Bacteriological Examination.

Chemical Investigation.

Benzidin Test for Occult Blood.

CULTURE OF TOOTH SOCKETS

INFECTIONS OF THE GENITAL TRACT

CEREBRO-SPINAL FLUID

NASAL, POST-NASAL, AND PHARYNGEAL SWABS

SPUTUM

EFFUSIONS INTO SEROUS CAVITIES

PUS

TISSUES FOR HISTOLOGICAL EXAMINATION

APPENDIX

COLLECTION OF PATHOLOGICAL MATERIAL

BLOOD

1. Blood for Widal and Wassermann Tests, and for the van den Bergh and Andrewes Diazo Reactions

For these purposes blood is best obtained from a vein by a syringe. It is advisable to obtain 2 c.cm. and to allow this to clot in a suitable specimen tube.

Technique of Venepuncture

The skin over the selected vein is cleansed with soap and water, dried, and swabbed with ether. The arm above is constricted by a tourniquet or by grip. The patient is instructed to clench and unclench the hand three or four times. In this way the vein will usually become prominent. It may then be steadied above the site of puncture while the syringe needle is inserted at as small an angle as possible to the skin. Care must of course be taken that the point of the needle does not pierce the far side of the vein. When the point of the needle is within the lumen of the vein, blood will flow into the syringe with little or no suction on the piston. Having withdrawn the desired quantity of blood, the constricting pressure is released before the needle is withdrawn. Firm pressure for a few minutes over the puncture will prevent further bleeding.

The syringe is emptied into the special tube and is washed out immediately. For the **Wassermann test** it is desirable to have serum free from laked corpuscles: it is therefore important, if the syringe has been sterilized by boiling, to wash it out with sterile normal saline before taking the specimen.

2. Blood for Blood Urea Estimation

One cubic centimetre of blood is obtained by a syringe from a vein as described, and emptied into an 'oxalated' tube. This is prepared by coating the interior of a tube

with a film of potassium oxalate solution, and evaporating to dryness.

3. Blood for Blood-sugar Estimation

If the blood can be examined within one or two hours it may be collected as for the blood urea estimation. Otherwise one of the following methods must be used:

(*a*) Blood, 0·1 c.cm., is drawn into a special pipette from a finger-prick, and is expelled on to a slip of specially prepared starch-free filter-paper. This is allowed to dry thoroughly at room temperature, and is then sent to the pathologist.

(*b*) Blood is collected in a tube containing a small quantity of a powder consisting of 0·5 gramme thymol and 5 grammes potassium fluoride. This prevents clotting and preserves the sugar content.

4. Blood-culture

Five to ten cubic centimetres of blood are obtained by venepuncture, especial care being taken to sterilize the skin and syringe and to avoid touching the site of the puncture or the needle with the fingers at any stage of the procedure.

There are three methods of disposing of the blood so obtained:

1. By the usual method the blood is distributed in quantities varying from about $\frac{1}{4}$ c.cm. to 1 c.cm. between six or more broth-tubes, great care being taken to avoid contamination during the procedure. In cases of suspected typhoid or paratyphoid infection it is advisable to add a tube of sterile bile, incubating this with about 5 c.cm. of blood.
2. The whole quantity is expelled into a flask containing 100 c.cm. of sterile peptone broth.

If either of these methods is used the specimens should be sent immediately by hand to the laboratory. The medium must not come in contact with the wool plugs during transit.

3. If the specimen must be sent by post to the laboratory, gelatin culture tubes can be used in place of broth-

tubes. The medium is melted and allowed to cool to about blood-heat before inoculation. The blood is mixed with the medium by rotating the tubes between the two hands. When setting has occurred they can then be safely transmitted by post.

5. Blood-count

It is useless to expect information of any value with regard to total numbers of red and white blood-cells from

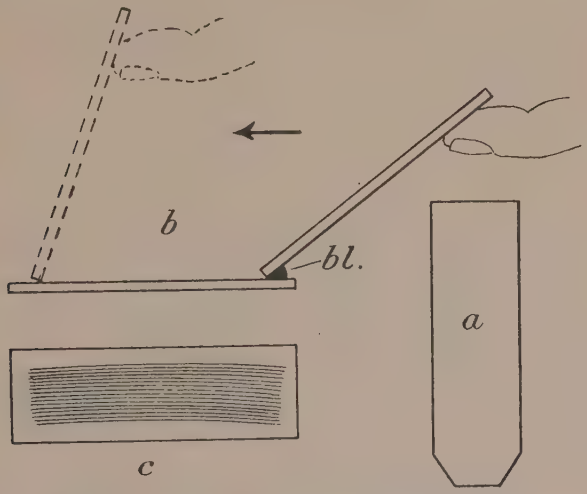


Fig. 6. *a*. The spreader: an ordinary slide, with an even edge, from which the two corners have been removed as shown. *b*. Method of holding the spreader in making the film. *bl*. The drop of blood. *c*. The film.

the practice of sending blood films to a pathologist. Information of value can sometimes be obtained in this way when pernicious anaemia or a leukaemia is present. It is not satisfactory to send diluted blood through the post for a blood-count.

Preparation of a Blood Film

For clinical purposes films are best made on slides. These must be cleaned by scrubbing with soap and water, rinsing, and drying with a clean handkerchief.

The lobe of an ear is cleaned with ether, dried, and pricked with a sterile Hagedorn needle. The first drop of blood is discarded and subsequent drops used. The blood should flow without undue squeezing.

A small drop of blood is placed close to one end of a clean slide, and this is laid on a flat table, drop uppermost. Immediately the edge of a spreader is applied to the drop, as shown in the diagram (Fig. 6). The spreader is not gripped, but is allowed to rest on the finger, as shown, and pushed to the other end of the slide. By having two straight edges to the smear, away from the edges of the slide, allowance can be made in counting for the tendency of cells of different sizes to accumulate in different parts of the film. Such films may be used for the detection of malarial parasites (see p. 13).

6. Blood for a Fragility Test, Coagulation Time, Enumeration of Blood Platelets, of Red Blood Corpuscles, and Reticulocyte Count

For these investigations it is advisable for the patient to be seen personally by the pathologist.

7. The Technique of the Haemoglobin Estimation and of the Leucocyte Count

As the practitioner frequently carries out haemoglobin and leucocyte estimations himself, the technique of these tests is described here.

Haemoglobin Estimation

Sahli's haemoglobinometer (Fig. 7) is recommended; its use is independent of a supply of coal gas, and it can be used by artificial light. The standard consists of a solution of acid haematin, prepared by the action of hydrochloric acid (A) on haemoglobin (C). In the graduated tube (B) N/10 hydrochloric acid is placed up to the mark 10. Having pricked the finger or ear in the usual way, 20 c.mm. of blood are sucked into the pipette (D) of the instrument, taking the precaution of removing excess of blood from the point of the pipette by cautiously wiping it with the finger.

The contents of the pipette are then emptied into the acid and the mixture gently shaken. In a minute or two the solution becomes clear and brown. It is then diluted with distilled water (E), adding a little at a time, and thoroughly mixing after each addition, until the colour matches the standard. A reading is taken, further distilled water is

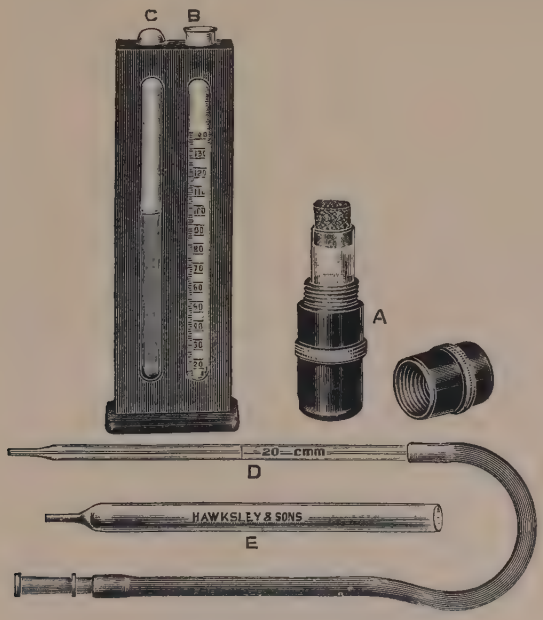
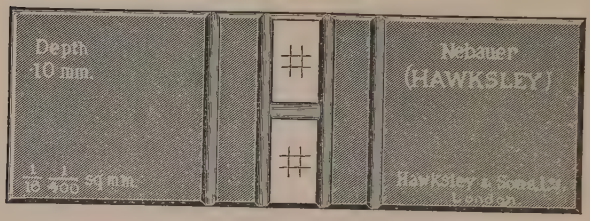


Fig. 7. Sahli's Haemoglobinometer.

added, a drop or two at a time, and then readings taken after each addition, until the two colours are definitely unequal. The mean of the equal readings gives the haemoglobin percentage of the normal. In this instrument the normal is 80: the reading must in that case be multiplied by $\frac{5}{4}$ to obtain the haemoglobin percentage figure.

Leucocyte Count

The white count pipette of the instrument, which gives a dilution of 1 in 10 or 1 in 20, is used. The finger or the lobe of an ear is cleansed as described above, pricked,



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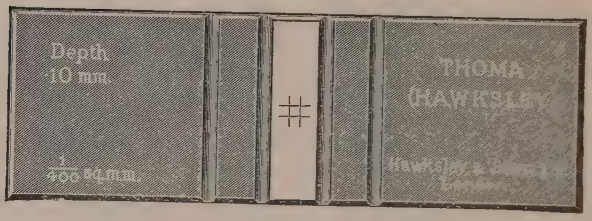

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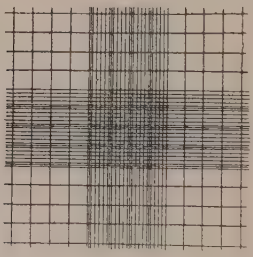

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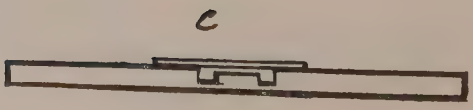

c

FIG. 8. *a*. Thoma-Levy counting chamber. *b*. Neubauer ruling. *c*. Diagram showing cover-slip in position, and open end of counting chamber.

and the first drop removed. Blood is then accurately taken into the pipette up to the mark 1 or 0·5. The pipette is filled to the mark 11 with the diluting fluid. This consists of 5 per cent. acetic acid coloured with methyl green, a solution which keeps indefinitely. A blood dilution of 1 in 10 or 1 in 20 is thus obtained. The filled pipette is well shaken, and the contents retained in safety by closing the two ends with a rubber band.

An open form of counting chamber, such as the Max Levy type, is recommended. The special feature of this instrument will be sufficiently obvious from the diagram.

The cover-slip is placed in position over the ruled area. The pipette is shaken again and the first drop or two, consisting of pure diluent, discarded. The point of the pipette is then applied to the open edge of the counting chamber, which is allowed to fill by capillarity. After a few minutes the cells will settle, and the preparation may be examined with the 1/6th objective of the microscope. The total number of leucocytes lying in a ruled area of known dimensions is to be counted. With the Neubauer ruling it is possible to count the number of cells lying in nine square millimetres, and from this the average number in one square millimetre is determined. This is equivalent to the number of cells in one-tenth of a cubic millimetre of diluted blood. The number in one cubic millimetre of undiluted blood is readily calculated.

THE FRACTIONAL TEST MEAL

Bennett recommends that the patient be given a glass of milk and a charcoal biscuit on the evening before the test, which is carried out early on the following morning.

The large stomach tubes formerly used have entirely given place to the narrow-bore tubes introduced by Rehfuss. Ryle's modification is shown in the diagram (Fig. 9). The end which is swallowed contains a small metal bulb, completely covered by the rubber; immediately above this are two large holes in the wall of the tubing.

The tube is first softened in hot water; the patient then swallows enough of it to bring the mark, which gives the

average distance from the teeth to the fundus of the stomach, between the teeth.

The resting fluid is then withdrawn by a record syringe attached to the free end of the tube. This specimen is placed in a specimen bottle and suitably labelled.

The patient must now drink the test meal, with the tube in position; it is advisable to keep this in position with tape or strapping so that it cannot be accidentally swallowed with the meal.

The usual test meal is a pint of oatmeal gruel, prepared by boiling two tablespoonfuls of oatmeal in a quart of water until the volume is reduced to one pint, and straining

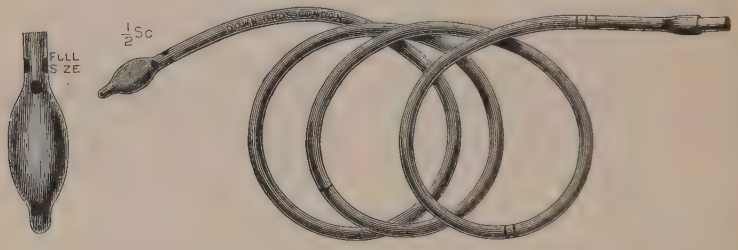

Fig. 9. Ryle's modification of the Rehfuss Tube.

through muslin. MacLean recommends a shredded wheat biscuit mixed up with a pint of water. One biscuit is ground to a powder, mixed with one pint of water, and boiled for 2–3 hours—the volume being maintained by periodic additions of water. The mixture is allowed to cool and is made up to one pint.

Ten cubic centimetres of stomach contents are then withdrawn at intervals of 15 minutes for 2 or $2\frac{1}{2}$ hours. If the stomach is not empty at this time, all that remains is removed. Each specimen is placed in a tube and appropriately labelled.

FAECES

For the following investigations a small portion of the stool is collected and transmitted in a container similar to that shown in the diagram.

1. General examination for blood, pus, epithelial cells, mucus, starch, fats, meat fibres, &c.
2. Bacteriological examination: amoeba cysts, ova of parasites.

In some cases, when the stool does not appear homogeneous, it may be wise to send the whole of one evacuation, so that the pathologist may choose the most suitable portion for examination.

3. Chemical investigations: occult blood, bile pigments, and derivatives.

Fig. 10. Specimen tube for faeces.

The whole evacuation should be sent when any of the following examinations are desired:

(*a*) Examination for macroscopic parasites.
(*b*) Examination for the presence of gall-stones.
(*c*) Examination for amoebae.
(*d*) Examination for tubercle bacilli.

The Benzidin Test for Occult Blood in the Faeces

Gregerson's Method

The following account is taken from A. G. Ogilvie's [1] paper. Powders are made up containing 0·2 gramme of barium peroxide and 0·025 gramme of pure benzidin; if put up in wax papers they will keep indefinitely. Just before

[1] See Reference 4, Section D.

the test one powder is dissolved in 5 c.cm. of a freshly prepared solution (50 per cent.) of acetic acid. A portion of the faeces is taken by means of a *clean* glass rod from the centre of the stool, and smeared on to a clean glass slide, and a few drops of the solution run on to the smear. A blue or blue-green colour develops within a minute if the test is positive.

CULTURES IN APICAL INFECTION OF TEETH

The most stringent precautions must be taken by the dental surgeon to ensure that the apex of the tooth is not contaminated by saliva during the process of extraction.

Before extraction, the tooth and surrounding tissues should be painted with iodine. The best method is for the pathologist to attend the extraction. If this is impracticable, the tooth should be wrapped in sterile gauze, or placed in a sterile tube, and sent as quickly as may be to the laboratory.

URINE

(*a*) **Ordinary Specimen.** This consists of urine mixed with organisms and cells from the urethra, and from the vagina in females. It is therefore useful for the routine physical and chemical investigations.[1]

(*b*) **Catheter Specimen.** This is essential for bacteriological and cytological purposes in the female. In males a satisfactory specimen can generally be obtained by meticulous cleansing of the glans penis with soap and water and by discarding the first few ounces passed. The rest of the act of micturition is made direct into a sterile bottle. An ordinary cork cannot be sterilized.

(*c*) **Twenty-four-hour Specimen.** This is needed for the detection of tubercle bacilli and for certain quantitative chemical investigations such as the estimation of the daily excretion of sugar, uric acid, diastase, and lead.

The urine is passed at, for example, 8 o'clock in the morning, and this specimen discarded. Each subsequent specimen, up to and including that passed at 8 o'clock the next

[1] Occasionally, the existence of a vaginal discharge is revealed by the presence of pus in an ordinary specimen of urine.

morning, is stored in a jar containing a few crystals of thymol, or a few cubic centimetres of chloroform. When estimation of diastase is required a few drops of toluol must be used. The total amount passed is recorded and a sample sent for analysis. This contains a proportion of all the constituents passed during twenty-four hours. For the detection of tubercle bacilli, the whole specimen should be sent to the laboratory.

INFECTIONS OF THE GENITAL TRACT

1. Prostatic Fluid

For investigation of infection of the prostate and posterior urethra, specimens are obtained as follows. First wash out the anterior urethra with boric-acid lotion and instruct the patient to pass urine into two specimen bottles. Pus in the posterior urethra will appear in the first of these specimens; pus in the second must have come from the bladder or kidney pelvis. The prostate is then massaged; a few drops of prostatic fluid are collected in a sterile tube for cultural purposes, and one or more films are made.

2. Pus from the Anterior Urethra

The pus is obtained either by a platinum loop or by a swab, and several thin films are made on clean slides; these are allowed to dry at room temperature.

3. Cervical Swab

In suspected gonorrhoea in the female a swab should be taken from the cervical discharge, the gonococcus being unlikely to be found in vaginal pus. A sterile speculum is introduced, vaginal secretion is mopped away, and the cervix carefully cleansed by sterile swabs before the cervical swab is introduced into the canal.

Films may be made direct, but should cultures be required, the swab must be kept warm and sent immediately to the laboratory.

CEREBRO-SPINAL FLUID

For technique of lumbar puncture, text-books should be consulted. The fluid should be collected in two sterile tubes

provided with rubber stoppers. The first few drops are liable to be blood-stained and should in that case be entirely discarded. The presence of blood interferes with the cell count, and therefore the fluid last collected is most suitable for this purpose.

NASAL, POST-NASAL, AND PHARYNGEAL SWABS

If swabs mounted on copper wire are used they will serve any of these purposes. To obtain a specimen from the post-nasal space, such a swab can readily be bent to a right angle, thus allowing the post-nasal area to be reached with ease.

SPUTUM

The mouth should be rinsed out well several times with boiled water before coughing up the specimen; a supply should be at hand for this purpose. The receptacle should be sterile. The sputum should be sent in as fresh a condition as possible to the laboratory. A special journey is often worth while if cultures are desired.

For tubercle bacilli an early morning specimen is frequently of most value.

EFFUSIONS INTO SEROUS CAVITIES

For the technique of paracentesis see text-books. Fluid for examination should be collected in two sterile tubes, one of which contains a little citrate or oxalate to prevent clotting.

PUS

In some cases, as for example actinomycosis, several cubic centimetres of the pus may give more information than will a simple smear or swab.

TISSUES FOR HISTOLOGICAL EXAMINATION

The specimen should be placed in at least five times its volume of 10 per cent. formalin saline.

i. e. Normal saline 90 parts.
Neutral formalin 10 parts.

It can be sent to the pathologist in this fixative in a securely corked wide-mouthed bottle of suitable size.

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